

# Exhibit 29

2011 FDA Supplemental Approval Letter to Danco  
Laboratories, LLC (June 6, 2011)



## DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

NDA 020687/S-014

**SUPPLEMENT APPROVAL**

Danco Laboratories, LLC

(b) (6)

P.O. Box 4816  
New York, NY 10185

Dear (b) (6):

Please refer to your Supplemental New Drug Application (sNDA) dated September 16, 2008, received September 17, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for MIFEPREX<sup>®</sup> (mifepristone) Tablets. We note that NDA 020687 is approved under the provisions of 21 CFR 314.520 (Subpart H).

This supplemental application provides for a proposed risk evaluation and mitigation strategy (REMS) for MIFEPREX (mifepristone) and was submitted in accordance with section 909(b)(1) of the Food and Drug Administration Amendments Act of 2007 (FDAAA). Under section 909(b)(1) of FDAAA, we identified MIFEPREX (mifepristone) as a product deemed to have in effect an approved REMS because there were in effect on the effective date of FDAAA, March 25, 2008, elements to assure safe use required under 21 CFR 314.520.

We acknowledge receipt of your amendments dated December 9, 2008, November 8, 2010, and May 19 and 27, 2011.

In accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for MIFEPREX (mifepristone) to ensure the benefits of the drug outweigh the risks of serious complications by requiring prescribers to certify that they are qualified to prescribe MIFEPREX (mifepristone) and are able to assure patient access to appropriate medical facilities to manage any complications.

Your proposed REMS, as amended and appended to this letter, is approved. The REMS consists of a Medication Guide, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

The REMS assessment plan will include the information submitted to FDA on May 27, 2011, and should include the following information:

- a. Per section 505-1(g)(3)(A), an assessment of the extent to which the elements to assure safe use are meeting the goal or goals to mitigate a specific serious risk listed in the labeling of the drug, or whether the goal or goals or such elements should be modified.
- b. Per section 505-1(g)(3)(B) and (C), information on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. With respect to any such postapproval study, you must include the status of such study, including whether any difficulties completing the study have been encountered. With respect to any such postapproval clinical trial, you must include the status of such clinical trial, including whether enrollment has begun, the number of participants enrolled, the expected completion date, whether any difficulties completing the clinical trial have been encountered, and registration information with respect to requirements under subsections (i) and (j) of section 402 of the Public Health Service Act. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 314.81(b)(2)(vii) and including any updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in section 505-1(g) could result in enforcement action.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in Section 505-1(g)(2)(A) of FDCA.

Prominently identify future submissions containing the REMS assessments or proposed modifications with the following wording in bold capital letters at the top of the first page of the submission:

**NDA 020687 REMS ASSESSMENT**

**NEW SUPPLEMENT FOR NDA 020687  
PROPOSED REMS MODIFICATION  
REMS ASSESSMENT**

**NEW SUPPLEMENT (NEW INDICATION FOR USE) FOR NDA 020687  
REMS ASSESSMENT  
PROPOSED REMS MODIFICATION (if included)**

If you do not submit electronically, please send 5 copies of REMS-related submissions.

As part of the approval under Subpart H, as required by 21 CFR 314.550, you must submit all promotional materials, including promotional labeling as well as advertisements, at least 30 days

before the intended time of initial distribution of the labeling or initial publication of the advertisement. Send one copy to the [REDACTED] (b) (6) and two copies of the promotional materials and the package insert directly to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications  
Food and Drug Administration  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

### **REPORTING REQUIREMENTS**

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, [REDACTED] (b) (6)

Sincerely,

*{See appended electronic signature page}*

[REDACTED] (b) (6)

### **ENCLOSURES:**

REMS Document  
REMS Materials

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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(b) (6)

06/08/2011

# Exhibit 30

2011 REMS for NDA 20-687 Mifeprex (mifepristone)  
Tablets, 200mg (June 8, 2011)



2. MIFEPREX will be dispensed only in certain health care settings, specifically clinics, medical offices, and hospitals.

Danco will ensure that MIFEPREX will only be available to be dispensed in a clinic, medical office, or hospital, by or under the supervision of a specially certified prescriber. MIFEPREX will not be distributed to or dispensed through retail pharmacies.

3. MIFEPREX will only be dispensed to patients with documentation of safe use conditions.

Danco will ensure that MIFEPREX will only be dispensed to patients with documentation of the following safe use conditions:

- a. The patient has completed and signed the Patient Agreement, and the Patient Agreement has been placed in the patient's medical record.
- b. The patient has been provided copies of the signed Patient Agreement and the Medication Guide.

C. Implementation System

The Implementation System will include the following:

1. Distributors who distribute MIFEPREX will be certified. To become certified, distributors must agree to:
  - a. Ship drug only to site locations identified by specially certified prescribers in signed Prescriber's Agreements, and maintain secure and confidential records of shipments.
  - b. Follow all distribution guidelines, including those for storage, tracking package serial numbers, proof of delivery, and controlled returns.
2. Danco will assess the performance of the certified distributors with regard to the following:
  - a. Whether a secure, confidential and controlled distribution system is being maintained with regard to storage, handling, shipping, and return of MIFEPREX.
  - b. Whether MIFEPREX is being shipped only to site locations identified by specially certified prescribers in the signed Prescriber's Agreement and only available to be dispensed to patients in a clinic, medical office, or hospital by or under the supervision of a specially certified prescriber.



3. If Danco determines the distributors are not complying with these requirements, Danco will take steps to improve their compliance.

D. Timetable for Submission of Assessments

Danco will submit REMS assessments to the FDA one year from the date of the approval of the REMS and every three years thereafter. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the assessment reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. Danco will submit each assessment so that it will be received by the FDA on or before the due date.

## MEDICATION GUIDE

**Mifeprex**<sup>®</sup> (MIF-eh-prex)  
(mifepristone)

Read this information carefully before taking Mifeprex\* and misoprostol. It will help you understand how the treatment works. This MEDICATION GUIDE does not take the place of talking with your health care provider (provider).

### What is Mifeprex?

**Mifeprex is used to end an early pregnancy.** It blocks a hormone needed for your pregnancy to continue. It is not approved for ending later pregnancies. Early pregnancy means it is 49 days (7 weeks) or less since your last menstrual period began. When you use Mifeprex (Day 1), you also need to take another medicine misoprostol, 2 days after you take Mifeprex (Day 3), to end your pregnancy. But, about 5-8 out of 100 women taking Mifeprex will need a surgical procedure to end the pregnancy or to stop too much bleeding.

### What is the most important information I should know about Mifeprex?

**What symptoms should I be concerned with?** Although cramping and bleeding are an expected part of ending a pregnancy, rarely, serious and potentially life-threatening bleeding, infections, or other problems can occur following a miscarriage, surgical abortion, medical abortion, or childbirth. Prompt medical attention is needed in these circumstances. Serious infection has resulted in death in a very small number of cases; in most of these cases misoprostol was used in the vagina. There is no information that use of Mifeprex and misoprostol caused these deaths. If you have any questions, concerns, or problems, or if you are worried about any side effects or symptoms, you should contact your provider. Your provider's telephone number is \_\_\_\_\_.

### Be sure to contact your provider promptly if you have any of the following:

**Heavy Bleeding.** Contact your provider right away if you bleed enough to soak through two thick full-size sanitary pads per hour for two consecutive hours or if you are concerned about heavy bleeding. In about 1 out of 100 women, bleeding can be so heavy that it requires a surgical procedure (surgical abortion/D&C) to stop it.

**Abdominal Pain or "Feeling Sick".** If you have abdominal pain or discomfort, or you are "feeling sick", including weakness, nausea, vomiting or diarrhea, with or without fever, more than 24 hours after taking misoprostol, you should contact your provider without delay. These symptoms may be a sign of a serious infection or another problem (including an ectopic pregnancy, a pregnancy outside the womb).

**Fever.** In the days after treatment, if you have a fever of 100.4°F or higher that lasts for more than 4 hours, you should contact your provider right away. Fever may be a symptom of a serious infection or another problem (including an ectopic pregnancy).

**Take this MEDICATION GUIDE with you.** When you visit an emergency room or a provider who did not give you your Mifeprex, you should give them your MEDICATION GUIDE so that

they understand that you are having a medical abortion with Mifeprex.

**What to do if you are still pregnant after Mifeprex with misoprostol treatment.** If you are still pregnant, your provider will talk with you about the other choices you have, including a surgical procedure to end your pregnancy. There is a chance that there may be birth defects if the pregnancy is not ended.

**Talk with your provider.** Before you take Mifeprex, you should read this MEDICATION GUIDE and sign a statement (PATIENT AGREEMENT). You and your provider should discuss the benefits and risks of your using Mifeprex.

## Who should not take Mifeprex?

Some women should not take Mifeprex. Do not take it if:

- It has been more than 49 days (7 weeks) since your last menstrual period began.
- You have an IUD. It must be taken out before you take Mifeprex.
- Your provider has told you that you have a pregnancy outside the uterus (ectopic pregnancy).
- You have problems with your adrenal glands (chronic adrenal failure).
- You take a medicine to thin your blood.
- You have a bleeding problem.
- You take certain steroid medicines.
- You cannot return for the next 2 visits.
- You cannot easily get emergency medical help in the 2 weeks after you take Mifeprex.
- You are allergic to mifepristone, misoprostol, or medicines that contain misoprostol, such as Cytotec or Arthrotec.

Tell your provider about all your medical conditions to find out if you can take Mifeprex. Also, tell your provider if you smoke at least 10 cigarettes a day.

## How should I take Mifeprex?

- **Day 1 at your provider's office:**
  - Read this MEDICATION GUIDE.
  - Discuss the benefits and risks of using Mifeprex to end your pregnancy.
  - If you decide Mifeprex is right for you, sign the PATIENT AGREEMENT.
  - After getting a physical exam, swallow 3 tablets of Mifeprex.
- **Day 3 at your provider's office:**
  - If you are still pregnant, take 2 misoprostol tablets.
  - Misoprostol may cause cramps, nausea, diarrhea, and other symptoms. Your provider may send you home with medicines for these symptoms.
- **About Day 14 at your provider's office:**
  - This follow-up visit is very important. You must return to the provider about 14 days after you have taken Mifeprex to be sure you are well and that you are not pregnant.
  - Your provider will check whether your pregnancy has completely ended. If it has not ended, there is a chance that there may be birth defects. If you are still pregnant, your provider will talk with you about the other choices you have, including a surgical procedure to end your pregnancy.

## **What should I avoid while taking Mifeprex and misoprostol?**

Do not take any other prescription or non-prescription medicines (including herbal medicines or supplements) at any time during the treatment period without first asking your provider about them because they may interfere with the treatment. Ask your provider about what medicines you can take for pain.

If you are breastfeeding at the time you take Mifeprex and misoprostol, discuss with your provider if you should stop breastfeeding for a few days.

## **What are the possible and reasonably likely side effects of Mifeprex?**

Cramping and bleeding are expected with this treatment. Usually, these symptoms mean that the treatment is working. But sometimes you can get cramping and bleeding and still be pregnant. This is why you must return to your provider on Day 3 and about Day 14. See “How should I take Mifeprex?” for more information on when to return to your provider. If you are not already bleeding after taking Mifeprex, you probably will begin to bleed once you take misoprostol, the medicine you take on Day 3. Bleeding or spotting can be expected for an average of 9–16 days and may last for up to 30 days. Your bleeding may be similar to, or greater than, a normal heavy period. You may see blood clots and tissue. This is an expected part of ending the pregnancy.

Other common symptoms of treatment include diarrhea, nausea, vomiting, headache, dizziness, back pain, and tiredness. These side effects lessen after Day 3 and are usually gone by Day 14. Your provider will tell you how to manage any pain or other side effects.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

## **When should I begin birth control?**

You can become pregnant again right after your pregnancy ends. If you do not want to become pregnant again, start using birth control as soon as your pregnancy ends or before you start having sexual intercourse again.

\* \* \*

Medicines are sometimes prescribed for purposes other than those listed in a MEDICATION GUIDE. For more information, ask your provider for the information about Mifeprex that is written for health care professionals. Ask your provider if you have any questions.

This MEDICATION GUIDE has been approved by the U.S. Food and Drug Administration.

Rev 3: 4/22/09

\*Mifeprex is a registered trademark of Danco Laboratories, LLC.

(Mifepristone) Tablets, 200 mg

## **PRESCRIBER'S AGREEMENT**

We are pleased that you wish to become a provider of Mifeprex\* (Mifepristone) Tablets, 200 mg, which is indicated for the medical termination of intrauterine pregnancy through 49 days from the first day of the patient's last menstrual period (see full prescribing information). Prescribing Information, Mifeprex Medication Guides and PATIENT AGREEMENT forms will be provided together with your order of Mifeprex.

Prior to establishing your account and receiving your first order, you must sign and return this letter to the distributor, indicating that you have met the qualifications outlined below and will observe the guidelines outlined below. If you oversee more than one office facility, you will need to list each facility on your order form prior to shipping the first order.

By signing the reverse side, you acknowledge receipt of the PRESCRIBER'S AGREEMENT and agree that you meet these qualifications and that you will follow these guidelines for use. You also understand that if you do not follow these guidelines, the distributor may discontinue distribution of the drug to you.

Under Federal law, Mifeprex must be provided by or under the supervision of a physician who meets the following qualifications:

- Ability to assess the duration of pregnancy accurately.
- Ability to diagnose ectopic pregnancies.
- Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or have made plans to provide such care through others, and are able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.
- Has read and understood the prescribing information of Mifeprex. The prescribing information is attached to this letter, and is also available by calling our toll free number, 1-877-4 Early Option (1-877-432-7596), or logging on to our website, [www.earlyoptionpill.com](http://www.earlyoptionpill.com).

In addition to these qualifications, you must provide Mifeprex in a manner consistent with the following guidelines.

- Under Federal law, each patient must be provided with a Medication Guide. You must fully explain the procedure to each patient, provide her with a copy of the Medication Guide and PATIENT AGREEMENT, give her an opportunity to read and discuss them, obtain her signature on the PATIENT AGREEMENT, and sign it yourself.
- The patient's follow-up visit at approximately 14 days is very important to confirm that a complete termination of pregnancy has occurred and that there have been no complications. You must notify Danco Laboratories in writing as discussed in the Package Insert under the heading DOSAGE AND ADMINISTRATION in the event of an on-going pregnancy which is not terminated subsequent to the conclusion of the treatment procedure.
- While serious adverse events associated with the use of Mifeprex are rare, you must report any hospitalization, transfusion or other serious event to Danco Laboratories, identifying the patient solely by package serial number to ensure patient confidentiality.
- Each package of Mifeprex has a serial number. As part of maintaining complete records for each patient, you must record this identification number in each patient's record.

Danco Laboratories, LLC  
 P.O. Box 4816  
 New York, NY 10185  
 1-877-4 Early Option (1-877-432-7596)  
[www.earlyoptionpill.com](http://www.earlyoptionpill.com)  
 \*MIFEPREX is a registered trademark of Danco Laboratories, LLC.

# ACCOUNT SETUP FORM

**MIFEPREX™ (Mifepristone) Tablets, 200 mg; NDC 64875-001-03**

## Billing information

Bill to Name \_\_\_\_\_  
 Address \_\_\_\_\_  
 City \_\_\_\_\_ State \_\_\_\_\_ ZIP \_\_\_\_\_  
 Phone \_\_\_\_\_ Fax \_\_\_\_\_  
 Attention \_\_\_\_\_

## Shipping information ☐ Check if same as above

Ship to Name \_\_\_\_\_  
 Address \_\_\_\_\_  
 City \_\_\_\_\_ State \_\_\_\_\_ ZIP \_\_\_\_\_  
 Phone \_\_\_\_\_ Fax \_\_\_\_\_  
 Attention \_\_\_\_\_

## Additional site locations

I will also be prescribing Mifeprex\* at these additional locations:

Name _____	Address _____
City _____	State _____ ZIP _____
Phone _____	Fax _____

Name _____	Address _____
City _____	State _____ ZIP _____
Phone _____	Fax _____

(Any additional sites may be listed on an attached sheet of paper.)

## Request additional materials

- ☐ Medication Guides ☐ Patient Agreements  
☐ State Abortion Guidelines ☐ Patient Brochures

## Establishing your account (required only with first order)

Each facility purchasing Mifeprex must be included on this form (see additional site locations box above) before the distributor can ship the product. Please read the Prescriber's Agreement on the reverse of this form and sign below.

**By signing below, you acknowledge receipt of the Prescriber's Agreement and agree that you meet these qualifications and that you will follow these guidelines for use.**

Print Name \_\_\_\_\_ Signature \_\_\_\_\_  
 Medical License # \_\_\_\_\_ Date \_\_\_\_\_

**Fax this completed Account Setup Form to the authorized distributor. Fax: 1-866-227-3343**

Please fax any questions to the above number or call 1-800-848-6142.

\*Mifeprex is a trademark of Danco Laboratories, LLC.

To set up your account:

**1**

Read the Prescriber's Agreement on the back of this Account Setup Form.

**2**

Complete and sign this form.

**3**

Fax the completed Account Setup Form to the Danco distributor at 1-866-227-3343. Your account information will be kept strictly confidential.

**4**

The distributor will call to finalize your account setup and take your initial order.

**5**

Subsequent orders may be phoned in and are usually shipped within 24 hours.

**6**

Unopened, unused product may be returned for a refund or exchange up to a year after the expiration date.



Mifeprex® (Mifepristone) Tablets, 200 mg

## PATIENT AGREEMENT

Mifeprex\* (mifepristone) Tablets

1. I have read the attached MEDICATION GUIDE for using Mifeprex and misoprostol to end my pregnancy.
2. I discussed the information with my health care provider (provider).
3. My provider answered all my questions and told me about the risks and benefits of using Mifeprex and misoprostol to end my pregnancy.
4. I believe I am no more than 49 days (7 weeks) pregnant.
5. I understand that I will take Mifeprex in my provider's office (Day 1).
6. I understand that I will take misoprostol in my provider's office two days after I take Mifeprex (Day 3).
7. My provider gave me advice on what to do if I develop heavy bleeding or need emergency care due to the treatment.
8. Bleeding and cramping do not mean that my pregnancy has ended. Therefore, I must return to my provider's office in about 2 weeks (about Day 14) after I take Mifeprex to be sure that my pregnancy has ended and that I am well.
9. I know that, in some cases, the treatment will not work. This happens in about 5 to 8 women out of 100 who use this treatment.
10. I understand that if my pregnancy continues after any part of the treatment, there is a chance that there may be birth defects. If my pregnancy continues after treatment with Mifeprex and misoprostol, I will talk with my provider about my choices, which may include a surgical procedure to end my pregnancy.
11. I understand that if the medicines I take do not end my pregnancy and I decide to have a surgical procedure to end my pregnancy, or if I need a surgical procedure to stop bleeding, my provider will do the procedure or refer me to another provider who will. I have that provider's name, address and phone number.
12. I have my provider's name, address and phone number and know that I can call if I have any questions or concerns.
13. I have decided to take Mifeprex and misoprostol to end my pregnancy and will follow my provider's advice about when to take each drug and what to do in an emergency.
14. I will do the following:
  - contact my provider right away if in the days after treatment I have a fever of 100.4°F or higher that lasts for more than 4 hours or severe abdominal pain.
  - contact my provider right away if I have heavy bleeding (soaking through two thick full-size sanitary pads per hour for two consecutive hours).
  - contact my provider right away if I have abdominal pain or discomfort, or I am "feeling sick", including weakness, nausea, vomiting or diarrhea, more than 24 hours after taking misoprostol.
  - take the MEDICATION GUIDE with me when I visit an emergency room or a provider who did not give me Mifeprex, so that they will understand that I am having a medical abortion with Mifeprex.
  - return to my provider's office in 2 days (Day 3) to check if my pregnancy has ended. My provider will give me misoprostol if I am still pregnant.
  - return to my provider's office about 14 days after beginning treatment to be sure that my pregnancy has ended and that I am well.

Patient Signature: \_\_\_\_\_

Patient Name (print): \_\_\_\_\_

Date: \_\_\_\_\_

The patient signed the PATIENT AGREEMENT in my presence after I counseled her and answered all her questions. I have given her the MEDICATION GUIDE for mifepristone.

Provider's Signature: \_\_\_\_\_

Name of Provider (print): \_\_\_\_\_



Date: \_\_\_\_\_

After the patient and the provider sign this PATIENT AGREEMENT, give 1 copy to the patient before she leaves the office and put 1 copy in her medical record. Give a copy of the MEDICATION GUIDE to the patient.

Rev 2: 7/19/05

\*Mifeprex is a registered trademark of Danco Laboratories, LLC.



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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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(b) (6)

06/08/2011

# Exhibit 31

2016 FDA Letter to Danco Laboratories re: NDA  
020687, Supp 20 (Mar. 29, 2016)



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

NDA 020687/S-020

**SUPPLEMENT APPROVAL**

Danco Laboratories, LLC

(b) (4), (b) (6)

P.O. Box 4816  
New York, NY 10185

Dear (b) (4), (b) (6) :

Please refer to your Supplemental New Drug Application (sNDA) dated May 28, 2015, received May 29, 2015, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Mifeprex (mifepristone) Tablets.

We acknowledge receipt of your risk evaluation and mitigation strategy (REMS) assessment dated July 17, 2015.

This "Prior Approval" supplemental new drug application proposes to provide for use through 70 days gestation, revise the labeled dose and dosing regimen and modify the REMS.

**APPROVAL & LABELING**

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

**CONTENT OF LABELING**

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert, text for the patient package insert, Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As at <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

### **REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for pre-menarcheal patients because the use of this product before menarche is not indicated, and we have determined that you have fulfilled the pediatric study requirement for post-menarcheal patients.

### **RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS**

The REMS for Mifeprex (mifepristone) Tablets was originally approved on June 8, 2011. The REMS consisted of a Medication Guide, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS. Your proposed modifications to the REMS included revisions to both the prescriber and patient agreement forms.

Other changes proposed in the efficacy supplement prompted additional revisions to the Mifeprex REMS materials. During review of this efficacy supplement, we also assessed the current REMS program to determine whether each Mifeprex REMS element remains necessary to ensure that the drug's benefits outweigh the risks.

After consultations between the Office of New Drugs (OND) and the Office of Surveillance and Epidemiology (OSE), we have determined that the approved REMS for Mifeprex should be modified to continue to ensure that the benefits of Mifeprex outweigh its risks and to minimize the burden on the healthcare delivery system of complying with the REMS. The REMS modifications submitted by you on March 29, 2016 are approved.

We have determined that it is no longer necessary to include the Medication Guide as an element of the approved REMS to ensure that the benefits of Mifeprex outweigh its risks. The

Medication Guide will continue to be part of the approved labeling in accordance with 21 CFR 208. Like other labeling, Medication Guides are subject to the safety labeling change provisions of section 505(o)(4) of the FDCA.

Your proposed modified REMS, submitted on July 17, 2015, and appended to this letter, is approved as amended. The modified REMS consists of elements to assure safe use (A, C and D), an implementation system, and a timetable for submission of assessments of the REMS.

The timetable for submission of assessments of the REMS remains the same as that approved on June 8, 2011.

The REMS assessment plan will include the information submitted to FDA on March 29, 2016.

The revised REMS assessment plan must include, but is not limited to, the following:

**REMS Assessment Plan**

1. Number of prescribers enrolled (cumulative)
2. Number of new prescribers enrolled during reporting period
3. Number of prescribers ordering Mifeprex during reporting period
4. Number of healthcare providers who attempted to order Mifeprex who were not enrolled; describe actions taken (during reporting period and cumulative).
5. Number of women exposed to Mifeprex (during reporting period and cumulative)
6. Summary and analysis of any program deviations and corrective action taken
7. Based on the information reported, an assessment and analysis of whether the REMS is meeting its goals and whether modifications to the REMS are needed

The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether 1 or more such goals or such elements should be modified.

We remind you that in addition to the REMS assessments submitted according to the timetable in the approved REMS, you must include an adequate rationale to support any proposed REMS modification for the addition, modification, or removal of any of goal or element of the REMS, as described in section 505-1(g)(4) of the FDCA.

We also remind you that you must submit a REMS assessment when you submit any future supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of the FDCA. This assessment should include:

- a) An evaluation of how the benefit-risk profile will or will not change with the new indication;
- b) A determination of the implications of a change in the benefit-risk profile for the current REMS;

- c) *If the new indication for use introduces unexpected risks:* A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.
- d) *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* A statement about whether the REMS was meeting its goals at the time of that the last assessment and if any modifications of the REMS have been proposed since that assessment.
- e) *If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* Provision of as many of the currently listed assessment plan items as is feasible.
- f) *If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rationale to support the modification, including:* Provision of the reason(s) why the proposed REMS modification is necessary, the potential effect on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan necessary to assess the proposed modified REMS. *If you are not proposing REMS modifications, provide a rationale for why the REMS does not need to be modified.*

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

**NDA 020687 REMS CORRESPONDENCE  
(insert concise description of content in bold capital letters, e.g.,  
UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT  
METHODOLOGY**

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.



Prominently identify any submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

**NDA 020687 REMS ASSESSMENT**

**NEW SUPPLEMENT FOR NDA 020687/S-000  
CHANGES BEING EFFECTED IN 30 DAYS  
PROPOSED MINOR REMS MODIFICATION**

*or*

**NEW SUPPLEMENT FOR NDA 020687/S-000  
PRIOR APPROVAL SUPPLEMENT  
PROPOSED MAJOR REMS MODIFICATION**

*or*

**NEW SUPPLEMENT FOR NDA 020687/S-000  
PRIOR APPROVAL SUPPLEMENT  
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABEL CHANGES  
SUBMITTED IN SUPPLEMENT XXX**

*or*

**NEW SUPPLEMENT (NEW INDICATION FOR USE)  
FOR NDA 020687/S-000  
REMS ASSESSMENT  
PROPOSED REMS MODIFICATION (if included)**

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

**REMS REVISIONS FOR NDA 020687**

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

If you do not submit electronically, please send 5 copies of REMS-related submissions.

NDA 020687/S-020  
Page 6

### **PROMOTIONAL MATERIALS**

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate: (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

OPDP Regulatory Project Manager  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion (OPDP)  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf> ).

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>.

Information and Instructions for completing the form can be found at

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

### **REPORTING REQUIREMENTS**

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call

(b) (6)

Sincerely,

*{See appended electronic signature page}*

(b) (6)

Center for Drug Evaluation and Research



ENCLOSURES:

Content of Labeling

REMS

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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(b) (6)

03/29/2016

# Exhibit 32

FDA, Center for Drug Evaluation and Research,  
Summary Review of Application Number:  
020687Orig1s020 (March 29, 2016)  
(2016 Summary Review)

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**020687Orig1s020**

**SUMMARY REVIEW**

## Summary Review for Regulatory Action

Date	March 29, 2016
Subject	Summary Review
NDA #/Supplement #	20687/S-020
Applicant name	Danco Laboratories, LLC
Date of submission	May 28, 2015
Date of submission receipt	May 29, 2015
PDUFA goal date	March 29, 2016
Proprietary name/established name	Mifeprex/mifepristone
Dosage form/strength	Oral tablet/200 mg
Dosage regimen	Mifeprex 200 mg tablet orally followed in 24-48 hours by 800 mcg buccal misoprostol
Proposed indication	Mifeprex is a progestin antagonist indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation
Action	Approval

1. Introduction
2. Background
3. CMC
4. Nonclinical Pharmacology/Toxicology
5. Clinical Pharmacology
6. Clinical Microbiology
7. Efficacy/Statistics
8. Safety
9. Advisory Committee Meeting
10. Pediatrics
11. Other Relevant Regulatory Issues
12. Labeling
13. Decision/Action/Risk Benefit Assessment

## 1. Introduction

Danco Laboratories, LLC, referred to hereafter as the Applicant, submitted an efficacy supplement (S-020) to NDA 20687 for Mifeprex (mifepristone). The Applicant sought the following changes to its approved application:

1. (b) (4) Decrease mifepristone dose from 600 to 200 mg, followed by misoprostol at a dose increased from 400 mcg to 800 mcg, administered buccally instead of orally; see below:
  - Day One: Mifeprex Administration (oral)  
One 200 mg tablet of Mifeprex is taken in a single oral dose
  - After a 24-48 hour interval: Misoprostol Administration (buccal)(minimum 24-hour interval between Mifeprex and misoprostol)  
Four 200 mcg tablets (total dose: 800 mcg) of misoprostol are taken by the buccal route
2. Removal of the instruction that administration of misoprostol must be done in-clinic, to allow for administration at home or other location convenient for the woman
3. Administration of misoprostol at 24-48 hours instead of 48 hours after Mifeprex
4. Follow-up, although still needed, not restricted to in clinic at 14 days after Mifeprex
5. Increase in the maximum gestational age from 49 days to 70 days
6. Change of the labeled time for expected expulsion of pregnancy from 4-24 hours to 2-24 hours post misoprostol administration
7. Addition that a repeat 800 mcg buccal dose of misoprostol may be used if needed
8. Change of “physician” to “healthcare provider” in the label and Risk Evaluation and Mitigation Strategies (REMS) document
9. Change in the indication statement to add reference to use of misoprostol: “Mifeprex is indicated, in a regimen with misoprostol, for the medical termination of pregnancy through 70 days gestation.”
10. Removal of references to “under Federal law” from the Prescriber’s Agreement under the REMS

## 11. Labeling changes addressing the pediatric requirements under the Pediatric Research Equity Act

This efficacy supplement submission includes information from published studies, review articles and additional information from the authors of some of the publications. These published studies evaluated reproductive age women in the U.S. and outside the U.S. who had early medical termination with mifepristone, in a regimen with misoprostol, including women up through 70 days of gestation.

This memorandum serves as the Division's decisional memorandum for the efficacy supplement.

## 2. Background

The active ingredient of Mifeprex, mifepristone, is a progestin antagonist. Mifeprex, in a regimen with misoprostol, is approved for the medical termination of pregnancy up through 49 days' gestation. The approved dosing regimen is currently labeled as follows:

- Day 1: The patient takes three 200 mg tablets of Mifeprex in a single oral dose in the clinic, medical office, or hospital.
- Day 3: The patient returns to the clinic, medical office, or hospital and takes two 200 mcg tablets of misoprostol orally.
- Day 14: The patient returns for a follow-up visit to confirm that a complete termination has occurred.

At the time of the September, 2000 approval, FDA restricted distribution of Mifeprex under 21 CFR 314.520, requiring that Mifeprex be dispensed only by or under the supervision of a physician who meets certain qualifications. With the passage of FDAAA in 2007, Mifeprex was deemed to have in effect an approved REMS. The Applicant submitted a formal REMS, which was approved on June 8, 2011 and consisted of the following: a Medication Guide, elements to assure safe use (ETASU A [special certification of healthcare providers who prescribe Mifeprex], ETASU C [dispensing only in certain healthcare settings], and ETASU D [safe use condition of a signed Patient Agreement]), an implementation system and a timetable for assessments. The goals of the REMS were 1) To provide information to patients about the benefits and risks of Mifeprex before they make a decision whether to take the drug and 2) To minimize the risk of serious complications by requiring prescribers to certify that they are qualified to prescribe Mifeprex and are able to assure patient access to appropriate medical facilities to manage any complications. The REMS for Mifeprex incorporated the restrictions under which the drug was originally approved.

Since 2011, the Applicant has submitted two REMS assessment reports. The Agency review of these reports determined that the REMS goals were being met and that no modifications were required to the REMS at that time.

FDA held a pre-NDA meeting with the Applicant on January 29, 2015, to discuss proposed labeling and REMS changes to be submitted in this efficacy supplement. These changes were submitted with the efficacy supplement.

The Applicant submitted published literature and supportive information to support changes to the dose, dosing regimen, gestational age, revisions to labeling, modifications to the REMS document, and to address PREA requirements. The Agency accepts the use of peer reviewed literature as primary data for an application under the framework of a 505(b)(2) application.

### 3. CMC

No new CMC information was submitted with this efficacy supplement. The CMC team determined no additional review or inspections were required. The CMC team completed a review of the labeling and found the CMC sections of labeling (sections 3, 11 and 16) acceptable (See review dated March 29, 2016). The CMC review team recommends approval of the efficacy supplement; refer also to the CMC review of the separate supplement proposing a single tablet blister pack for Mifeprex, dated January 11, 2016. There are no outstanding CMC issues or postmarketing commitments or requirements.

***Comment:** On March 10, 2016, a separate CMC supplement was approved that allowed the packaging of individual 200 mg tablets of mifepristone; previously packaging consisted of three 200 mg tablets per blister pack (a total of 600 mg Mifeprex as administered under the originally approved dosing regimen).*

### 4. Nonclinical Pharmacology/Toxicology

No new nonclinical information was submitted in this supplement. The Pharmacology/Toxicology team revised labeling to conform to the Pregnancy and Lactation Labeling Rule. There are no outstanding nonclinical issues. The Pharmacology/Toxicology review team recommends approval of the efficacy supplement; refer to the Pharmacology/Toxicology review dated March 4, 2016.

### 5. Clinical Pharmacology

The Applicant did not conduct any new clinical pharmacology studies pertaining to the proposed (b) (4) regimen, but provided information on pharmacokinetics (PK) of misoprostol following various routes of administration. The PK of the 200 mg Mifeprex tablet has not been characterized in women, but data are available in men and were submitted in the original NDA. The Clinical Pharmacology review team determined that the PK data were appropriate for inclusion in labeling. Review of the labeling pertinent to the Clinical Pharmacology sections is complete and labeling relevant to pharmacokinetics and pharmacodynamics is acceptable. There are no outstanding Clinical Pharmacology issues or postmarketing commitments or requirements. The clinical pharmacology review team recommends approval of the efficacy supplement; refer to the Clinical Pharmacology review dated March 29, 2016.



## 6. Clinical Microbiology

Not applicable.

## 7. Efficacy/Statistics

The Applicant submitted published literature as the primary evidence to support the efficacy (and safety) of the proposed dosing regimen (refer to the Clinical Review dated March 29, 2016, Section 9.5 for a list of submitted references). Most published articles submitted by the Applicant and reviewed by the clinical review team reported the primary efficacy endpoint as complete termination of pregnancy without further medical or surgical intervention; the Division considers this to be a clinically relevant endpoint.

The majority of the publications included a statement that the study was conducted under institutional review board (IRB) or Ethical Review Committee approval and the women gave informed consent. The clinical review team concluded that the published literature was adequate as the primary information source to support the changes proposed in the efficacy supplement. During the course of the review, the team also requested and received more detailed information from select publications from their authors via communication with the Applicant.

Although there were slight demographic differences among the published studies from the database, these differences were not expected to alter the efficacy or safety of Mifeprex. Therefore, for the majority of the proposed efficacy changes, the clinical team assessed efficacy information from a subset of publications that evaluated a given proposed change. An independent statistical review was not needed for this review of published literature.

The clinical review team identified several major proposed clinical changes in the efficacy supplement. As these major changes are interrelated, in some cases data from a given study were relied on to provide evidence to support multiple changes. These major changes as considered by the clinical team included:

1. A proposed dosing regimen consisting of mifepristone 200 mg orally followed by the buccal administration of 800 mcg misoprostol including:
  - a. Use of a revised interval between mifepristone and misoprostol from 48 hours to 24-48 hours
  - b. Allowing home administration of misoprostol
  - c. Use of an additional dose of misoprostol
2. Support for extending the gestation age through 70 days
3. Flexibility in follow-up visit: follow-up is needed in the range of 7-14 days after Mifeprex administration; the specific nature and exact timing of the follow-up to be agreed upon by the healthcare provider and patient.
4. Change in who can provide Mifeprex from physician to healthcare provider who prescribes

The following section summarizes the clinical review team's evaluations that supported the above proposed changes:

1. *Support for the proposed dose and dosing regimen of 200 mg of Mifeprax orally and 800 mcg of misoprostol buccally 24-48 hours after Mifeprax administration:*  
The clinical review team reviewed the submission and identified studies and review articles that evaluated over 35,000 women who were treated with efficacy in the 91-98% range. For additional details on the efficacy from these studies, please refer to Section 6 of the Clinical Review.
2. *Support for extending the gestational age to 70 days:*  
The Applicant submitted a number of published articles and systematic reviews that supported the proposed dose and dosing regimen. Four studies and one systematic review evaluated the exact proposed dosing regimen through 70 days gestation. These include three prospective observational studies (Winikoff et al 2012<sup>1</sup>, Boersma et al<sup>2</sup>, Sanhueza Smith et al<sup>3</sup>) and one randomized controlled trial (RCT) (Olavarrieta et al<sup>4</sup>) that had a primary objective of evaluating medical abortion provision by non-physicians. The systematic review by Chen and Creinin<sup>5</sup> covered 20 studies including over 30,000 women; all but one of the studies used the proposed regimen in gestations through 70 days (the remaining study used 400 mcg of buccal misoprostol). For those publications that provided overall success rates, these were in the range of 97-98%. Other relevant publications include the systematic review by Raymond<sup>6</sup> of 87 studies, which covered a variety of misoprostol doses and routes of administration used with 200 mg of mifepristone. Assessing the efficacy by misoprostol dose, the paper noted that doses  $\geq$  800 mcg had a success rate of 96.8%, with an ongoing pregnancy rate of 0.7%.

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<sup>1</sup> Winikoff B, Dzuba IG, Chong E, et al. Extending outpatient medical abortion services through 70 days of gestational age. *Obstet Gynecol* 2012; 120: 1070-6

<sup>2</sup> Boersma AA, Meyboom-de Jong B, Kleiverda G. Mifepristone followed by home administration of buccal misoprostol for medical abortion up to 70 days of amenorrhoea in a general practice in Curacao. *Eur J Contracept Reprod Health Care* 2011; 16: 61-6

<sup>3</sup> Sanhueza Smith P, Pena M, Dzuba IG, et al. Safety, efficacy and acceptability of outpatient mifepristone-misoprostol medical abortion through 70 days since last menstrual period in public sector facilities in Mexico City. *Reprod Health Matters* 2015; 22: 75-82

<sup>4</sup> Olavarrieta CD, Ganatra B, Sorhaindo A, Karver TS, Seuc A, Villalobos A, Garcia SG, Pérez M, Bousiequez M, Sanhueza P. Nurse versus physician-provision of early medical abortion in Mexico: a randomized controlled non-inferiority trial. *Bull World Health Organ* 2015; 93: 249-258

<sup>5</sup> Chen MJ, Creinin MD. Mifepristone with Buccal Misoprostol for Medical Abortion *Obstet Gynecol*: a Systematic Review. *Obstet Gynecol* 2015; 126(1): 12-21

<sup>6</sup> Raymond EG & Grimes DA. The comparative safety of legal induced abortion and childbirth in the United States. *Obstet Gynecol* 2012; 119: 215-9

The original dosing regimen specifies taking misoprostol 2 days after Mifeprex. This efficacy supplement proposes a more flexible time frame of 24 to 48 hours between Mifeprex and misoprostol administration. Data from a review article by Wedisinghe et al<sup>7</sup> evaluated different time intervals using administration of misoprostol after Mifeprex. A meta-analysis of all five studies found a non-significant odds ratio for failure for shorter vs. longer dosing intervals, but a trend for lower success if a dosing interval < 8 hours is used. Chen & Creinin's systematic review<sup>8</sup> of 20 studies including over 33,000 women, all but one using the proposed regimen, compared the success of dosing intervals of 24 hours with intervals ranging from 24-48 hours. The success rate in six studies that used a 24-hour interval through 63 days gestation was 94.2%, compared to the rate of 96.8% in 14 studies that used a 24-48 hour interval, and this difference was statistically significant. The clinical team concluded that the efficacy of the revised dosing regimen was not compromised by revising the dosing interval to 24-48 hours. In addition, they noted that the overall rate of ongoing pregnancies did not differ significantly by dosing interval.

3. *Administration of misoprostol after Mifeprex administration at home:* Currently, the dosing regimen specifies that misoprostol is taken in the clinic setting following Mifeprex administration. No specific publication evaluated treatment outcomes with use of misoprostol at home compared to in-clinic dosing. However, one large literature review (Raymond et al<sup>9</sup>) evaluated a variety of mifepristone treatment regimens with different misoprostol doses, routes of administration and dosing intervals used in gestations through 63 days. Roughly half of the studies included in this review did not require women to take misoprostol in-clinic. Rates of treatment failure and of ongoing pregnancy were very similar regardless of whether misoprostol was taken in-clinic or at another location. The clinical review team concluded that the review provided sufficient data to support labeling that misoprostol does not need to be restricted to in-clinic administration.
4. *Use of a repeat misoprostol dose, if necessary:* The Applicant submitted several published studies that supported use of a repeat misoprostol dose, when complete uterine expulsion did not occur after the initial misoprostol dose following Mifeprex. In clinical practice, the usual treatment for incomplete expulsion (retained products of conception) may include either a repeat dose of misoprostol, expectant management or a surgical procedure (suction aspiration or a dilation and curettage). Studies that specifically report the success rate of a repeat dose of misoprostol are:

<sup>7</sup> Wedisinghe L and Elsandabesee D. Flexible mifepristone and misoprostol administration interval for first-trimester medical termination. *Contraception* 2010; 81(4): 269-74. doi: 10.1016/j.contraception.2009.09.007. Epub Oct 29, 2009

<sup>8</sup> Creinin MD, Fox MC, Teal S, Chen A, Schaff EA, Meyn LA. MOD Study Trial Group: A randomized comparison of misoprostol 6-8 hours versus 24 hours after mifepristone for abortion. *Obstet Gynecol* 2004; 103: 851-859

<sup>9</sup> Raymond EG & Grimes DA. The comparative safety of legal induced abortion and childbirth in the United States. *Obstet Gynecol* 2012; 119: 215-9

- Winikoff et al<sup>10</sup> – studied the proposed regimen through 70 days gestation; of the few women who received a second dose for an incomplete abortion at follow-up, the success rate was 91% at 57-63 days and 67% at 64-70 days.
- Chen and Creinin<sup>11</sup> – a systematic review of 20 studies, all but one of which used the proposed regimen up through 70 days; success of a second dose ranged from 91-100%
- Boersma et al<sup>12</sup> – included pregnancies through 70 days treated with the proposed regimen; five of 330 women took a second dose due to absence of bleeding 48 hours after first dose; the success rate was 80%
- Louie et al<sup>13</sup> – studied the proposed regimen to 63 days; in 16 women (of 863) who took a second dose of misoprostol, the success rate was 100%
- Chong et al<sup>14</sup> – compared the proposed regimen to a lower dose of misoprostol; the success of a second dose of misoprostol was 92% overall, but the number of women in each dose arm getting a second dose was not specified.
- Winikoff et al<sup>15</sup> – 14 women in the proposed regimen took a second dose of misoprostol with a success rate of 92.9%.

Using the information from the above studies and other supportive data, the clinical team concluded that the available data support the efficacy of a repeat dose of misoprostol if complete expulsion has not occurred. The relatively high complete pregnancy termination rates indicate that this option is likely to reduce the need for a surgical intervention.

5. *Requirements regarding follow-up care:* Current labeling states that women will return to the clinic 14 days after Mifeprex administration for follow-up. This provision was based on the follow up regimen in the U.S. phase 3 trial that supported the initial approval in 2000. Although the Applicant submitted several studies that evaluated flexibility in the time of follow-up, the key publication identified by the review team that addressed this issue was a 2013 article by

<sup>10</sup> Winikoff B, Dzuba IG, Chong E, et al. Extending outpatient medical abortion services through 70 days of gestational age. *Obstet Gynecol* 2012; 120: 1070-6

<sup>11</sup> Creinin MD, Fox MC, Teal S, Chen A, Schaff EA, Meyn LA. MOD Study Trial Group: A randomized comparison of misoprostol 6-8 hours versus 24 hours after mifepristone for abortion. *Obstet Gynecol* 2004; 103: 851-859

<sup>12</sup> Boersma AA, Meyboom-de Jong B, Kleiverda G. Mifepristone followed by home administration of buccal misoprostol for medical abortion up to 70 days of amenorrhoea in a general practice in Curacao. *Eur J Contracept Reprod Health Care* 2011; 16: 61-6

<sup>13</sup> Louie KS, Tsereteli T, Chong E, Ailyeva F, Rzayeva G, Winikoff B. Acceptability and feasibility of mifepristone medical abortion in the early first trimester in Azerbaijan. *Eur J Contracept Reprod Health Care* 2014; 19(6): 457-464

<sup>14</sup> Chong E, Tsereteli T, Nguyen NN, Winikoff B. A randomized controlled trial of different buccal misoprostol doses in mifepristone medical abortion. *Contraception* 2012; 86: 251-256

<sup>15</sup> Winikoff B, Dzuba IG, Creinin MD, Crowden WA, Goldberg AB, Gonzales J, Howe M, Moskowitz J, Prine L, Shannon CS. Two distinct oral routes of misoprostol in mifepristone medical abortion: a randomized controlled trial. *Obstet Gynecol* 2008; 112(6): 1303-1310



Raymond<sup>16</sup>. The impact of the timing of follow-up was assessed in Raymond's systematic review of studies using various treatment regimens. While some have posited that earlier follow-up may result in a higher rate of surgical intervention (for women who would have had complete expulsion had they been given a bit more time), Raymond's analyses found no difference in failure rates for women followed less than one week after mifepristone as compared to a week or more after mifepristone. As follow-up was anticipated to not alter the efficacy of the proposed dosing regimen, this change is also discussed below in Section 7.

6. *Allowing qualified healthcare providers to use Mifeprex.*

The Applicant provided data on the efficacy of medical abortion provided by non-physician healthcare providers, including four studies with 3,200 women in randomized controlled clinical trials and 596 women in prospective cohorts. These studies included a study by Warriner et al<sup>17</sup> that showed efficacy of 97.4% with nurses versus 96.3% by physicians.

**Conclusions:** I concur with the clinical review team's assessments and conclusions and these conclusions will be reflected in labeling. The data and information reviewed constitute substantial evidence of efficacy to support the proposed dosing regimen for Mifeprex for pregnancy termination through 70 days gestation. Other proposed changes to the Mifeprex labeling, including the time interval between Mifeprex and misoprostol dosing, and use of a repeat dose, were also adequately supported by evidence. Finally, I concur with the clinical review team that the information from the published literature also supported efficacious use of Mifeprex by non-physician providers.

**Comment:** Discussion was held as to whether the original dosing regimen approved in 2000 (i.e., Mifeprex 600 mg and misoprostol 400 mcg up to 49 days gestation) should remain in labeling. (b) (4)

(b) (4) the clinical review team and I concur with their (b) (4) request to remove the current regimen from the labeling. Removal of the original dosing regimen simplifies labeling, and avoids any confusion regarding instructions. Therefore, the revised labeling, and REMS materials accompanying the approval of this efficacy supplement, will include only the proposed dosing regimen and instructions. It should be noted that there are no safety or efficacy concerns about the originally approved dosing regimen that led to removing it from the labeling.

<sup>16</sup>Raymond EG, et al. First-trimester medical abortion with mifepristone 200 mg and misoprostol: a systematic review. *Contraception* 2013;87(1):26-37.

<sup>17</sup>Warriner IK, Wang D, Huong NTM, Thapa K, Tamang A, Shah I et al. Can midlevel health-care providers administer early medical abortion as safely and effectively as doctors? A randomized controlled equivalence trial in Nepal. *Lancet* 2011; 377: 1155-61.

## 8. Safety

The safety of the proposed dosing regimen for Mifeprex was supported by the evidence from submitted published literature and postmarketing experience. The focus of the safety analysis was on published studies that evaluated the proposed dosing regimen (Mifeprex 200 mg followed by 800 mcg misoprostol buccally 24-48 hours later), with comparison to the known safety profile of the currently approved dosing regimen.

*Exposure:* Per the Applicant's submission, the clinical review concluded that there have been approximately 2.5 million uses of Mifeprex by U.S. women since the drug's approval in 2000. The clinical review team estimated that exposure to the proposed dosing regimen for their safety analysis was based on approximately 30,000 patients (refer to Table 11 for a list of references used to evaluate safety). Such exposure volume is sufficient to characterize the safety profile of the proposed dosing regimen and other proposed changes in this efficacy supplement.

*Deaths:* Deaths with medical abortion rarely occur and causality can be difficult to determine. Most of the publications did not specifically report any deaths with medical abortion with Mifeprex. Among the seven U.S. studies submitted to support the safety profile of Mifeprex and misoprostol, only one (Grossman, et al<sup>18</sup>) explicitly addressed deaths and noted that there were no deaths among 578 subjects evaluated in the study. Only one observational study (Goldstone, et al<sup>19</sup>) from Australia contained a report of a death after a mifepristone and misoprostol dosing regimen. In this retrospective review of 13,345 pregnancy terminations, the authors identified one death from sepsis. The article stated that the death was in an individual who failed to follow-up with her healthcare provider despite showing signs of illness. Based on this information, deaths in association with abortion are extremely rare.

Deaths reported from the postmarketing experience of Mifeprex are summarized below in the Postmarketing Experience section.

*Nonfatal serious adverse events:* The clinical review team identified key nonfatal serious adverse events (SAEs) associated with the proposed dosing regimen for Mifeprex. These SAEs include: hospitalization, serious infection, bleeding requiring transfusion and ectopic pregnancy. Section 7 of the clinical review dated March 29, 2016, provides a detailed discussion of reported rates of hospitalization, serious infection, bleeding requiring transfusion and ectopic pregnancy. The latter is not an adverse reaction because an ectopic pregnancy would exist prior to the Mifeprex regimen; it represents instead a failure to diagnose an ectopic pregnancy. Overall rates identified by the clinical review team from the published literature are as follows:

- Hospitalization: 0.04-0.6% in U.S. studies of over 14,000 women; 0-0.7% in international studies of over 1,200 women

<sup>18</sup>Grossman D, Grindlay K, Buchacker T, Lane K, Blanchard K. Effectiveness and acceptability of medical abortion provided through telemedicine. *Obstet Gynecol* 2011;118:296-303.

<sup>19</sup>Goldstone P, Michelson J, Williamson E. Early medical abortion using low-dose mifepristone followed by buccal misoprostol: A large Australian observational study. *Med J Austral* 2012; 197: 282-6.

- Serious infection/sepsis: 0-0.2% in U.S. and international studies of over 12,000 women
- Transfusion: 0.03-0.5% in U.S. studies of over 17,000 women; 0-0.1% in international studies of over 12,000 women

A study by Upadhyay et al<sup>20</sup> reported a 0.31% rate of major complications (including incomplete or failed abortion, hemorrhage, infection or uterine perforation that required hospitalization, surgery or transfusion) for medical abortions (dosing regimen unspecified) through 63 days; this was about double the rate reported for first trimester aspiration abortions and statistically significantly higher. However, these rates were driven by higher rates of incomplete/failed abortion; rates of hemorrhage (0.14%) and infection (0.23%) did not differ from those associated with aspirations.

Only one submitted study reported an ectopic pregnancy. This study (Winikoff et al<sup>21</sup>) reported one ectopic among 847 women (0.12%).

**Comment:** The proposed dosing regimen has been studied extensively in the literature using U.S. and global sites. Serious adverse events including deaths, hospitalization, serious infections, bleeding requiring transfusion and ectopic pregnancy are rarely reported. The rates of these serious adverse events are well below 1% and do not suggest a safety profile different from the original approved Mifeprex dosing regimen. Although there is less serious adverse event data on women who received Mifeprex and misoprostol between 64-70 days of gestation, the data from a U.S. study of 379 women (Winikoff et al)<sup>22</sup> in that gestational age is reassuring that the rates of these serious adverse events are not clinically different from that of other gestational age ranges.

In summary, based on the published literature, nonfatal serious adverse events occur with Mifeprex and misoprostol use with rates generally less than 1%. Increased gestational age (64-70 weeks) was not associated with an increased incidence of nonfatal SAEs. Other submission- specific safety issues that were evaluated including uterine rupture and angioedema/anaphylaxis are discussed in the Postmarketing Experience section below.

**Loss to follow-up:** The studies included in this safety review revealed a wide range of loss to follow-up, from 0.6% loss to follow-up in the study with telephone follow-up (Ngoc et al<sup>23</sup>) to 22% in the Grossman et al<sup>24</sup> study using telemedicine to deliver medical

<sup>20</sup>Upadhyay UD, Desai S, Lidar V, Waits TA, Grossman D, Anderson P, Taylor D. Incidence of emergency department visits and complications after abortion. *Obstet Gynecol* 2015;125(1):175-183.

<sup>21</sup>Winikoff B, Dzuba IG, Creinin MD, Crowden WA, Goldberg AB, Gonzales J, Howe M, Moskowitz J, Prine L, Shannon CS. Two distinct oral routes of misoprostol in mifepristone medical abortion: a randomized controlled trial. *Obstet Gynecol* 2008;112(6):1303-1310.

<sup>22</sup>Winikoff B, Dzuba IG, Chong E, et al. Extending outpatient medical abortion services through 70 days of gestational age. *Obstet Gynecol* 2012;120:1070-6.

<sup>23</sup>Ngoc NTN, et al. Acceptability and feasibility of phone follow-up after early medical abortion in Vietnam: A randomized controlled trial. *Obstet Gynecol* 2014;123:88-95.

<sup>24</sup>Grossman D, Grindlay K, Buchacker T, Lane K, Blanchard K. Effectiveness and acceptability of medical abortion provided through telemedicine. *Obstet Gynecol* 2011;118:296-303.



abortion services.

**Comment:** Based on these data reviewed by the clinical review team, there is no literature that suggests that follow-up modality alters safety. Therefore, labeling will not be directive regarding follow-up; that will be a decision left to the patient and provider.

**Common adverse events:** The clinical review team evaluated common adverse reaction data and compared U.S. and global study locations. The comparison revealed that there were differences in the frequency of common adverse reactions, with the reporting rates considerably higher among the U.S. studies. There is no reason to anticipate regional differences in the safety profile for the same treatment regimen, so these differences likely reflect lower ascertainment or subject reporting of adverse reactions in non-U.S. studies. Regardless, inclusion of this non-U.S. data in labeling would not be appropriate, as it is unlikely to be informative to the U.S. population of users. The data to be reported in labeling is outlined in Table 1 below:

**Table 1: Common Adverse Events ( $\geq 15\%$ ) in U.S. Studies of the Proposed Dosing Regimen**

Adverse Reaction	# U.S. studies	Number of Evaluable Women	Range of frequency (%)	Upper Gestational Age of Studies Reporting Outcome
Nausea	3	1,248	51-75%	70 days
Weakness	2	630	55-58%	63 days
Fever/chills	1	414	48%	63 days
Vomiting	3	1,248	37-48%	70 days
Headache	2	630	41-44%	63 days
Diarrhea	3	1,248	18-43%	70 days
Dizziness	2	630	39-41%	63 days

Source: Data from Middleton<sup>25</sup>, Winikoff<sup>26</sup> and Winikoff<sup>27</sup> as outlined in Table 2 of the CDTL review dated March 29, 2016.

One concerning adverse event is severe vaginal bleeding. Severe vaginal bleeding can result in interventions such as hospitalization and transfusion and may be associated with infection. The overall rate of bleeding across publications varied between 0.5% and 4.2%. Two publications (Sanhueza Smith et al<sup>28</sup> and Gatter et al<sup>29</sup>) evaluated clinically significant bleeding by gestational age. Although the publications reported slightly different rates, there was no trend of increased bleeding requiring intervention with Mifeprex and misoprostol use with increasing gestational age.

<sup>25</sup> Middleton T, et al. Randomized trial of mifepristone and buccal or vaginal misoprostol for abortion through 56 days of last menstrual period. *Contraception* 2005; 72: 328-32

<sup>26</sup> Winikoff B, Dzuba IG, Chong E, et al. Extending outpatient medical abortion services through 70 days of gestational age. *Obstet Gynecol* 2012; 120: 1070-6

<sup>27</sup> Winikoff B, Dzuba IG, Creinin MD, Crowden WA, Goldberg AB, Gonzales J, Howe M, Moskowitz J, Prine L, Shannon CS. Two distinct oral routes of misoprostol in mifepristone medical abortion: a randomized controlled trial. *Obstet Gynecol* 2008; 112(6): 1303-1310

<sup>28</sup> Sanhueza Smith P, Pena M, Dzuba IG, et al. Safety, efficacy and acceptability of outpatient mifepristone-misoprostol medical abortion through 70 days since last menstrual period in public sector facilities in Mexico City. *Reprod Health Matters* 2015;22:75-82.

<sup>29</sup> Gatter M, Cleland K, Nucatola DL. Efficacy and safety of medical abortion using mifepristone and buccal misoprostol through 63 days. *Contraception* 2015; 91:269-273.



**Comment:** While not all of the studies reported common adverse events, those that reported did not have unexpected rates of common adverse events. These common adverse events are included in labeling in section 6.1 (Clinical Trial Experience) in the ADVERSE REACTIONS section.

*Postmarketing experience – Spontaneous reports:*

The safety profile for Mifeprex includes over 15 years of postmarketing safety data available on Mifeprex due to the reporting requirements under the REMS. The Year 3 REMS Assessment report was submitted by the Applicant in June, 2015. The (b) (6) provided a comprehensive review of adverse event reports submitted from 2000 through November 17, 2015. Findings include:

- No Clostridial septic deaths reported in the U.S. since 2009, and none worldwide since 2010.
- The postmarketing rates of hospitalization, severe infection, blood loss requiring transfusion and ectopic pregnancy reported from publications and remain stable and relatively low.

*Submission-specific safety issues:*

- Anaphylaxis/angioedema: The (b) (6) (b) (6) identified a safety signal of anaphylaxis and angioedema with mifepristone administration. This signal was based on a comprehensive review of adverse event reports submitted from 2000 through November 17, 2015. A FAERS search retrieved one case of anaphylaxis and six cases of angioedema with mifepristone administration. Six of the seven cases were seen in women using mifepristone for termination of pregnancy. Six of the seven cases noted some type of medical intervention, such as treatment with an antihistamine, a histamine H2 antagonist, a corticosteroid, or a combination of various medications. Hospitalization was noted in three of the seven total cases; all three hospitalization cases occurred in patients who experienced angioedema. There were no additional cases of anaphylaxis or angioedema identified in the literature.

**Comment:** (b) (6) and the clinical review team recommended that anaphylaxis and angioedema be described in the Contraindications and Adverse Reactions sections of labeling. These labeling sections were discussed with the Applicant and labeling was revised for those sections to describe these serious adverse events.

- Uterine rupture: As discussed in the clinical review, the potential risk of uterine rupture was considered because the current labeling for misoprostol includes a Boxed Warning against the use of misoprostol for gestations more than 8 weeks due to the risk of uterine rupture. Although misoprostol is used alone for various obstetric indications, including induction of labor at term, it was important to consider whether labeling about this potential risk is warranted for Mifeprex. Both the clinical reviewer and the (b) (6) (b) (6) reviewed the literature and (b) (6) searched FAERS for adverse event reports.



Published literature reported three case reports<sup>30,31,32</sup> of uterine rupture with mifepristone/misoprostol treatment in the first trimester. Of these three reports, two patients had a risk factor for uterine rupture (prior uterine surgery). The third case was in a patient who received more than two doses of misoprostol. After consideration, the clinical review team decided that labeling should include information about this event. The FAERS search did not identify any reports of uterine rupture with use of mifepristone alone. Of 80 reports, 77 cited use of misoprostol alone, and three of mifepristone and misoprostol. Only two reports of uterine rupture in the first trimester were identified, both using misoprostol alone; one entailed an unspecified dose and route of misoprostol at 5 weeks gestation, and one involved vaginal administration of 800 mcg misoprostol at 8 weeks gestation for cervical preparation prior to a surgical abortion in a woman with a prior uterine scar.

Based on the available safety reports of uterine rupture, the review team from (b) (6) and clinical review team concluded that these data demonstrated that uterine rupture with Mifeprex and misoprostol in the first ten weeks (70 days) of gestation is exceedingly uncommon, and occurs most often in the face of a risk factor (previous uterine surgery).

**Comment:** I agree with the clinical review team and the (b) (6) team that the risk of uterine rupture with first trimester use of mifepristone and misoprostol appears to be extremely rare, and most often associated with a prior uterine scar, a known risk factor for uterine rupture. Labeling of these reports is included in section 2.3 of the DOSAGE AND ADMINISTRATION and section 6.2 of the ADVERSE REACTIONS of labeling to provide additional information to healthcare providers, but no restriction of use is needed based upon this extremely rare adverse reaction.

The clinical review team also evaluated the safety for each of the following major changes proposed in this efficacy supplement:

1. Changing the dosing interval between Mifeprex and misoprostol from 48 hours to 24-48 hours
2. Home administration of misoprostol
3. Use of a repeat dose of misoprostol
4. Change in the follow-up timeframe and method of follow-up
5. Allowing providers other than physicians to provide Mifeprex

<sup>30</sup>Khan S et al. Uterine rupture at 8 weeks' gestation following 600 µg of oral misoprostol for management of delayed miscarriage. Journal of Obstet Gynaecol 2007; 27: 869-870

<sup>31</sup> Bika O, Huned D, Jha S, Selby K Uterine rupture following termination of pregnancy in a scarred uterus J Obstet Gynaecol 2014; 34(2): 198-9. doi: 10.3109/01443615.2013.841132

<sup>32</sup> Willmott F, et al. Rupture of uterus in the first trimester during medical termination of pregnancy for exomphalos using mifepristone/misoprostol. BJOG 2008;15:575-77

To evaluate each of these changes, the reviewers evaluated the adverse event information regarding:

- Changing the timing interval between Mifeprax and misoprostol and change in the gestational age to 70 days:* Support for the 24-48 hour interval and use up through 70 days was primarily based on a large systematic review by Shaw et al<sup>33</sup>. This review evaluated studies looking at different follow-up modalities and demonstrated that there are a variety of acceptable alternatives to in-clinic follow-up that can identify cases in which there is need for additional intervention. In addition, the systematic review did not identify any significant difference in adverse events with different time intervals. Based on these findings, labeling will not be directive regarding specific details of how follow-up should be performed; this will be a decision between the patient and her healthcare provider.
- Home administration of misoprostol:* The Applicant supplied several published studies that supported this change including Gatter et al<sup>34</sup> and Ireland et al<sup>35</sup>. These studies reported on large numbers of women in the U.S. who took misoprostol at home. The authors showed that home administration of misoprostol, as part of the proposed regimen, is associated with exceedingly low rates of serious adverse events, and with rates of common adverse events comparable to those in the studies of clinic administration of misoprostol that supported the initial approval in 2000. Given that information is available on approximately 45,000 women from the published literature, half of which incorporated home use of misoprostol, there is no clinical reason to restrict the location in which misoprostol may be taken. Given the fact that the onset of cramping and bleeding occurs rapidly (i.e., generally within 2 hours) after misoprostol dosing, allowing dosing at home increases the chance that the woman will be in an appropriate and safe location when the process begins.
- Use of a repeat dose of misoprostol:* Safety reporting from studies that evaluated a repeat dose of misoprostol did not specifically assess the subset of women who received a second dose, but no unexpected findings were identified. One randomized controlled trial (Coyaji et al<sup>36</sup>) conducted in 300 women seeking medical abortion in India looked at a single misoprostol dose as compared to two misoprostol doses. Although there was no difference in the complete pregnancy termination rate in women who received a second misoprostol dose compared to those who did not, the repeat misoprostol dose reduced the need for surgical intervention. This study was reassuring in that there was no significant difference in the adverse events observed—similar percentages of women experienced

<sup>33</sup> Shaw KA, Topp NJ, Shaw JG, Blumenthal PB. Mifepristone-misoprostol dosing interval and effect on induction abortion times. *Obstet Gynecol* 2013;121(6):1335-1347.

<sup>34</sup> Gatter M, Cleland K, Nucatola DL. Efficacy and safety of medical abortion using mifepristone and buccal misoprostol through 63 days. *Contraception* 2015; 91:269-273.

<sup>35</sup> Ireland LD, Gatter M, Chen AY. Medical compared with surgical abortion for effective pregnancy termination in the first trimester. *Obstet Gynecol* 2015;126:22-8.

<sup>36</sup> Coyaji K, Krishna U, Ambardekar S, Bracken H, Raote V, Mandlekar A, Winikoff B. Are two doses of misoprostol after mifepristone for early abortion better than one? *BJOG* 2007;114:271-278.

cramping (87% in the single dose group, 89% in the repeat dose group), nausea (both groups 1%), vomiting (both groups 0%), and diarrhea (0% in the single dose group versus 2% in the repeat dose group). A supportive systematic review by Gallo et al<sup>37</sup> also provided safety information on subjects who received repeat misoprostol. In this review, the only side effects discussed in the trials were diarrhea, which was more common on those groups receiving misoprostol orally than in those receiving it exclusively vaginally (26-27% versus 9%). Rash was reported <1%. Based on these findings, labeling will be changed because the misoprostol dose does not need to be restricted to in clinic administration to assure safe pregnancy termination using the proposed dosing regimen. Given the onset of bleeding and cramping after misoprostol, allowing home administration increases the likelihood that a woman will be in an appropriate and safe location when the pregnancy termination process begins.

- *Change in the follow-up timeframe and method of follow-up:* The Applicant submitted several articles that described different methodologies in follow-up including phone calls and standardized instructions. The clinical reviewers evaluated a study in Scotland by Cameron et al<sup>38</sup> that evaluated self-assessment as compared to standard follow-up methodologies (clinic visit or phone call). Most of the women chose self-assessment over an in-clinic visit or phone call, and there were no significant differences in adverse outcomes between women who underwent self-assessment of health compared to those who had a clinic visit or phone call. Among women with an ongoing pregnancy after Mifeprex and misoprostol, the majority self-identified and presented within two-weeks for care. Based on this information and the other data from the Raymond systematic article<sup>39</sup> that did not identify a difference in failure rate for earlier (less than one week) as compared to one week or greater of follow-up, sufficient support was provided to use a broadened window of 7 to 14 days for follow-up. This revised follow-up time frame will be included in labeling.
- *Allowing providers other than physicians to provide Mifeprex:* The current Prescriber's Agreement in the REMS specifies that "...Mifeprex must be provided by or under the supervision of a physician who meets the following qualifications..." In addition, current labeling states that Mifeprex will be supplied only to licensed physicians who sign and return a Prescriber's Agreement. However, labeling states that other healthcare providers, acting under the supervision of a qualified physician, may also provide Mifeprex to patients. Several published studies submitted by the Applicant indicate that health care providers such as nurse practitioners, nurse midwives, and physician assistants are

<sup>37</sup> Gallo MF, Cahill S, Castelman L, Mitchell EMH. A systematic review of more than one dose of misoprostol after mifepristone for abortion up to 10 weeks gestation. *Contraception* 2006;74:36-41.

<sup>38</sup> Cameron ST, Glasier A, Johnstone A, Dewart H, Campbell A. Can women determine the success of early medical termination of pregnancy themselves? *Contraception* 2015;91:6-11.

<sup>39</sup> Raymond EG & Grimes DA. The comparative safety of legal induced abortion and childbirth in the United States. *Obstet Gynecol* 2012; 119: 215-9



currently providing abortion services. One of these studies (Kopp Kallner et al<sup>40</sup>) was a randomized controlled trial of 1,068 women in Sweden who were randomized to receive medical abortion care from two nurse midwives experienced in medical terminations and trained in early pregnancy ultrasound versus a group of 34 physicians with varying training and experience. Success rates were  $\geq 96\%$  regardless of gestational age. The nurse midwife group had few complications, though this was not statistically significant (4.1% for nurse midwives, versus 6.1% for doctors,  $p=0.14$ ). No serious complications were reported and no blood transfusions were administered in the study. Based on this and other supportive studies, the information supports the efficacy and safety of allowing healthcare providers other than physicians can effectively and safely provide abortion services, provided that they meet the requirements for certification described in the REMS. The clinical team also felt that the term “healthcare provider who prescribes” would be the appropriate terminology as prescribing ability is a critical factor in dispensing Mifeprex.

The clinical review team concluded that the evidence demonstrated acceptable safety for each of the above proposed changes, and I concur with their conclusion. The proposed dosing regimen has a similar safety profile as the original regimen approved in 2000. Adverse outcomes of interest, such as deaths, serious infection, transfusions, ectopic pregnancies and uterine rupture, remain rare, and are not necessarily attributable to Mifeprex use. Overall, the rate of deaths and nonfatal serious adverse events are acceptably low, and data for the proposed regimen do not suggest a safety profile that deviates from that of the originally approved regimen. No association between adverse outcomes and increasing gestational age was identified. Finally, the available information supports the safety of the other proposed changes, including increasing the flexibility of the time interval between Mifeprex and misoprostol, at home use of misoprostol, use of a repeat dose of misoprostol, change in the follow-up timeframe and allowing health care providers other than physicians to prescribe and dispense Mifeprex were acceptable.

## 9. Advisory Committee Meeting

Mifeprex is not a new molecular entity requiring discussion before an advisory committee. In addition, an advisory committee was not necessary as the application did not raise complex scientific or other issues that would warrant holding an AC before approval.

## 10. Pediatrics

This efficacy supplement triggered requirements under the Pediatric Research Equity Act (PREA). The Agency granted a partial PREA waiver for pre-menarcheal females ages birth to 12 years because it would be impossible to conduct studies in this pediatric population, as pregnancy does not exist in premenarcheal females.

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<sup>40</sup> Kopp Kallner H, Fiala C, Stephansson O, Gemzell-Danielsson K. Home self-administration of vaginal misoprostol for medical abortion at 50-63 days compared with gestation of below 50 days. *Human Reprod* 2010;25(5):1153-1157.

The Applicant fulfilled the remaining PREA requirement in postmenarcheal females by submitting published studies of Mifeprex for pregnancy termination in postmenarcheal females less than 17 years old. Efficacy and safety information in these adolescents was based on a U.S. study in 322 postmenarcheal adolescents (Gatter et al<sup>41</sup>). Of the 322 adolescents, 106 of these adolescents were under 16; see Table 2 below:

**Table 2: Age and Number of Adolescents Undergoing Medical Abortion (Gatter et al<sup>42</sup>)**

Age of Subject	Number of Subjects evaluated
11	1
12	1
13	2
14	20
15	82
16	216

Source: Refer to Table 17 of the Medical Officer's review dated March 29, 2016

The Gatter et al<sup>43</sup> study reported that postmenarchal females less than 18 years old had a 98.7% pregnancy termination rate as compared to females aged 18-24, who had a rate of 98.1%. This article reported that loss to follow-up was slightly higher in those less than 18 years old, however, age did not adversely impact efficacy outcomes.

One issue was whether adolescents would comply with at home use of misoprostol. The Gatter<sup>44</sup> et al study incorporated at home use of misoprostol into the Mifeprex dose regimen given to all females, including postmenarchal females less than 18 years old. The overall efficacy in adolescents was similar to that of all older women. This information supports at home administration of misoprostol in postmenarchal females under 17.

Two other published studies provided additional efficacy on Mifeprex use by adolescents for pregnancy termination:

- Phelps et al<sup>45</sup> evaluated data from 28 adolescents aged 14 to 17, at ≤ 56 days gestation, using Mifeprex 200 mg followed 48 hours later by misoprostol 800 mcg vaginally. In this study, 100% of subjects had a complete pregnancy termination, with five not requiring misoprostol.

<sup>41</sup>Gatter M, Cleland K, Nucatola DL. Efficacy and safety of medical abortion using mifepristone and buccal misoprostol through 63 days. *Contraception* 2015; 91:269-273.

<sup>42</sup> Ibid.

<sup>43</sup>Gatter M, Cleland K, Nucatola DL. Efficacy and safety of medical abortion using mifepristone and buccal misoprostol through 63 days. *Contraception* 2015; 91:269-273.

<sup>44</sup>Gatter M, Cleland K, Nucatola DL. Efficacy and safety of medical abortion using mifepristone and buccal misoprostol through 63 days. *Contraception* 2015; 91:269-273.

<sup>45</sup>Phelps RH, et al. Mifepristone abortion in minors. *Contraception* 2001;64:339-343.

- Niinimaki et al<sup>46</sup> used data from a Finnish Registry from 2000-2006. An analysis of efficacy between adolescents under age 18 compared to the women  $\geq$  age 18 indicated that the adolescent group had a lower rate of incomplete abortions as compared to adults. And efficacy outcomes in adolescents were similar to those of adult women.

The safety of Mifeprex in postmenarcheal adolescents was primarily supported by adverse event information from the Gatter et al<sup>47</sup> study. (b) (6), (b) (4)

Supportive data from a Finnish registry (Niinimaki et al ) from 3024 adolescent females under 18 years of age reported that, compared to adult women, the risks of hemorrhage (adjusted odds ratio 0.87 [95% confidence interval: 0.77 to 0.99]), incomplete abortion (0.69, [95% confidence interval: 0.59 to 0.82]), and surgical evacuation (0.78, [95% confidence interval: 0.67 to 0.90]) were lower in the adolescent cohort. In the Finnish registry study, a majority of adolescents and adults received both Mifeprex and misoprostol. Safety findings from the Gatter et al and Niinimaki et al studies are reassuring and indicate that the safety profile of Mifeprex is similar between postmenarcheal adolescents and adult women.

Additional details from this article and other published data on Mifeprex use in adolescents (females under 17) are described in the clinical review (Refer to the Medical Officer's review dated March 29, 2016).

(b) (6) concurred that the efficacy and safety data in postmenarcheal adolescents less than 17 years old was sufficient to support the use of Mifeprex in this pediatric population and to fulfill the PREA pediatric study requirement. The revised Mifeprex labeling will state that that efficacy and safety are similar to adult women in the Pediatric Use section (8.4).

## 11. Other Relevant Regulatory Issues

(b) (6)

(b) (6) reviewed the Medication Guide in conjunction with the (b) (6) (b) (6). Both (b) (6) and (b) (6) found the Medication Guide to be acceptable with recommended changes (See review dated March 29, 2016). The Division considered all of the recommendations from (b) (6) in revising and updating the text in

<sup>46</sup>Niinimaki M, et al. Comparison of rates of adverse events in adolescent and adult women undergoing medical abortion: population register based study. BJM 2011;342: d2111.

<sup>47</sup>Gatter M, Cleland K, Nucatola DL. Efficacy and safety of medical abortion using mifepristone and buccal misoprostol through 63 days. Contraception 2015; 91:269-273.

<sup>48</sup>Niinimaki M, et al. Comparison of rates of adverse events in adolescent and adult women undergoing medical abortion: population register based study. BJM 2011;342: d2111.



the Medication Guide and incorporated appropriate changes into the final agreed upon Medication Guide.

(b) (6) (b) (6)

(u) (o) reviewed the Prescribing Information (PI) in addition to the joint review with (b) (6) of the Medication Guide in conjunction with (b) (6). After review, (b) (6) provided recommended changes (See (b) (6) review dated March 29, 2016). The Division considered all of the recommendations from (b) (6) in revising and updating the text in the PI and incorporated appropriate changes into the final label.

(b) (6) (b) (6)

(b) (6) (b) (6) in the (b) (6) (b) (6) reviewed the proposed modifications to the REMS. The (b) (6) review reflected agreement with the Applicant's proposed REMS changes which include:

- Removal of the term "under Federal law" from the Prescriber's Agreement.
- Replacement of the word "physician" with a broader term to describe appropriate healthcare professionals who may order, prescribe and administer Mifeprex. (b) (6) believes that the Applicant's proposed terminology of " (b) (4) " is too broad and that a more appropriate description is "healthcare provider who prescribes," which limits acceptable healthcare providers to those who are licensed in their state to prescribe medications.
- Removal of the Medication Guide from the REMS. The Medication Guide remains an important education tool for patients. It will still be dispensed to each patient in accordance with 21 CFR part 208. As described in the Medication Guide Guidance, a Medication Guide is not necessary to ensure that the benefits outweigh the risks of Mifeprex.
- Modification of Element to Assure Safe Use (ETASU) A, the Prescriber's Agreement. (b) (6) recommends changing the name of the document to the Prescriber's Agreement Form to be consistent with other REMS programs. References to "physician" should be changed to "healthcare provider who prescribes."
- (b) (6) recommends removing the Patient Agreement from the REMS for a number of reasons:
  1. The established safety profile over 15 years of experience with Mifeprex is well-characterized, stable, and known serious risks occur rarely
  2. The Medication Guide contains the same risk information addressed in the Patient Agreement, and will still be provided to patients under 21 CFR part 208
  3. The Prescriber's Agreement Form will continue to require providers to explain the treatment, its effects and risks associated with Mifeprex and to answer any questions that a patient may have
  4. Established clinical practice provides for counseling, informing the patient about follow-up, when to contact the provider/clinic, answering questions and obtaining signed informed consent before treatment. FDA has removed REMS



requirements in other programs based on the integration of the REMS safe use condition into clinical practice.

Other revisions to the REMS document will be made for consistency with changes described above and to reflect current FDA thinking and practice regarding format, language and flow in REMS documents. These changes include modification of the Mifeprex REMS goal, changes in requirements to certify prescribers (removal of the requirement to obtain a Patient Agreement) and other minor edits.

In summary, the overall (b) (6) recommendation for the REMS modification for this efficacy supplement was approval (Refer to (b) (6) review dated March 29, 2016).

## 12. Labeling

Carton and container labeling was reviewed by the (b) (6) (b) (6) (b) (6) (b) (6) and the (b) (6) (b) (6) (b) (6) (b) (6) Their comments were conveyed to the Applicant as appropriate.

The label was submitted in the format prescribed by the PLR. Although the supplement was submitted prior to when it would otherwise have been required to comply with the PLLR requirements, the review team believed it would be of value to harmonize with this labeling standard to the extent possible.

Specific issues discussed during labeling negotiations included the selection of studies for inclusion in Section 6.1 (Clinical Trial Experience in the ADVERSE REACTIONS section) and 14 (CLINICAL STUDIES section). Only studies that evaluated the specific proposed regimen were included in these sections. For the Adverse Reactions section, examination of the common adverse reaction data by U.S. compared to non-U.S. study location revealed that there were large differences in the frequency of common adverse reactions, with the reporting rate considerably higher among the U.S. studies. This may reflect differences in ascertainment or subject reporting of adverse reactions in non-U.S. studies. Regardless, inclusion of this non-U.S. data would not be appropriate, as it is unlikely to be informative to the U.S. population of users. In the case of serious adverse reactions, the reported frequency was quite similar regardless of study location; for this reason, serious adverse reaction information from global studies is reported. Agreement on labeling was reached on March 29, 2016.

Post-Marketing Requirement/Commitment and Risk Evaluation and Mitigation Strategies (REMS):

*Postmarketing Requirements/Postmarketing Commitments:* None.

*Risk Evaluation and Mitigation Strategies (REMS):* The Applicant proposed a REMS modification for the Mifeprex REMS program with the submission of this efficacy supplement. The review teams from the (b) (6) evaluated the current Mifeprex REMS program and the proposed REMS modifications to determine whether each Mifeprex REMS element remains necessary to ensure that the benefits of Mifeprex outweigh the risks. Factors that impacted the decision included findings from two REMS assessments (the more recent REMS assessment review was completed in October 2015), an unchanged safety profile, and published literature that documented adequate safeguards in clinical practice with the use of Mifeprex in a regimen with misoprostol.

The teams determined that the following REMS modifications were warranted:

1. Revisions to the Prescriber Agreement Form to reflect the new dosing regimen and to reflect current REMS formatting and language standards
2. Removal of the Medication Guide as a REMS element, as distribution of the Medication Guide is required under 21 CFR 208
3. Removal of the Patient Agreement as a Documentation of Safe Use Condition (ETASU D)
4. Updating of the REMS goals to reflect the above 3 changes.
5. Removal of the phrase “Under Federal law” from the Prescriber’s Agreement
6. Replacing the term “licensed physician” with “healthcare provider who prescribes”

The above modifications to the Mifeprex REMS program were discussed with the (b) (6) (b) (6) on January 15, 2016, as per (b) (6).

The (b) (6) concurred with conforming changes to the Prescriber’s Agreement to reflect the new dosing regimen, and with removal of the Medication Guide from the REMS. The Medication Guide would remain a part of labeling to inform patients about the risks associated with Mifeprex use. The (b) (6) also concurred with revisions to the REMS goals to reflect these changes.

The (b) (6) concurred with the removal of the term “under Federal law”. A rationale for the original inclusion of the phrase “Under Federal law” cannot be discerned from available historical documents, nor is it consistent with REMS materials for other products. All the conditions of approval, including the REMS materials, are under Federal law; therefore, the phrase is unnecessary and it was decided that the phrase be removed from the Prescriber’s Agreement.



The (b) (6) concurred with use of the term “healthcare providers who prescribe.” To support a change in the REMS that would allow qualified healthcare providers other than physicians to prescribe Mifeprex through the Mifeprex REMS program, the Applicant provided information from over 3,200 women in randomized controlled trials and 596 women in prospective cohort studies comparing medical abortion care by physicians versus other providers (nurses or nurse midwives). These studies were conducted in a variety of settings (international, urban, rural, and low-resource). No differences in serious adverse events, ongoing pregnancy or incomplete abortion were identified between the groups. Given that providers other than physicians are providing family planning and abortion care under supervision and that the approved labeling and REMS program stipulate that prescribers must be able to refer patients for additional care, including surgical management, allowing these prescribers to participate in the Mifeprex REMS program is acceptable.

The (b) (6) also concurred with the teams’ recommendation to remove the Patient Agreement (ETASU D) from the REMS although some (b) (6) members commented that additional support for the review team’s rationale for this modification was needed. The review team’s rationale for this change was:

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- The safety profile of Mifeprex is well-characterized over 15 years of experience, with known risks occurring rarely; the safety profile has not changed over the period of surveillance.
- Established clinical practice includes patient counseling and Informed Consent, and, more specifically with Mifeprex, includes counseling on all options for termination of pregnancy, access to pain management and emergency services if needed.
- Medical abortion with Mifeprex is provided by a well-established group of organizations and their associated providers who are knowledgeable in this area of women's health. Their documents and guidelines cover all the safety information that also appears in the Patient Agreement.
- ETASUs A and C remain in place: The Prescriber's Agreement under ETASU A requires that providers "explain the procedure, follow-up, and risks to each patient and give her an opportunity to discuss them." The REMS will continue to require that Mifeprex be dispensed to patients only in certain healthcare settings, specifically, clinics, medical offices, and hospitals. This ensures that Mifeprex can only be dispensed under the direct supervision of a certified prescriber.
- Labeling mitigates risk: The Medication Guide, which will remain a part of labeling, contains the same risk information covered under the Patient Agreement.

The Mifeprex REMS program will have a modified ETASU REMS that will continue to ensure that Mifeprex can only be prescribed by certified prescribers and be dispensed to patients in certain healthcare settings, specifically, clinics, medical offices and hospitals. The Medication Guide will continue to be distributed to patients required under 21 CFR part 208. As required for all ETASU REMS, ongoing assessments of the Mifeprex REMS program will continue to ensure that the modified Mifeprex REMS program is meeting its goals.

### **13. Decision/Action/Risk Benefit Assessment**

#### **Decision:**

All regulatory and scientific requirements have been adequately addressed in this efficacy supplement. Review teams involved in this supplement have recommended approval of the supplement from their disciplines' perspective. The submitted efficacy and safety information supported approval of the proposed dosing regimen through 70 days gestation, and other changes discussed in this summary memo. This supplement will receive an Approval action.

#### **Benefit Risk Assessment:**

This efficacy supplement provided substantial evidence of efficacy for the proposed dosing regimen through 70 days gestation. The efficacy findings were similar to those that led to the approval of the original dosing regimen in 2000. In addition, the submitted published literature supported other changes sought in this efficacy supplement that will

be reflected in labeling: 1) a more flexible time interval of 24 to 48 hours between Mifeprex and misoprostol administration, 2) the option of at home administration of misoprostol, 3) the option of repeat misoprostol dosing, if clinically indicated, 4) flexibility in the follow-up time frame of 7 to 14 days, and 5) permitting qualified healthcare providers other than physicians to prescribe Mifeprex.

The safety findings of the proposed dosing regimen were acceptable and were similar to those seen with the original dosing regimen approved in 2000.

After review of the REMS modifications proposed by the Sponsor, I concur with the clinical team and (b) (6) recommendations that:

1. The Medication Guide can be removed from the Mifeprex REMS program. The Medication Guide requirements under 21 CFR part 208 require the Medication Guide to be distributed to patients. Mifeprex will only be dispensed by a healthcare professional who will be knowledgeable and able to provide the patient instructions on appropriate use of the drug, including what potential side effects may occur or follow-up that may be required as appropriate, and who will answer any questions the patient may have. In that setting, the Medication Guide will already be a required available tool for counseling. Therefore, given the existing requirements under 21 CFR part 208, I concur that there is no reason for the Medication Guide to specifically be a part of the REMS.
2. The Prescriber Agreement Form (ETASU A) as revised reflects current FDA format and content to conform to current REMS programs and reflect the labeling changes that will be approved in this supplement. I concur that the changes are acceptable.
3. Revision of the Mifeprex REMS goals (ETASU C) will adequately mitigate the risk of serious complications by requiring certification of healthcare providers who prescribe and ensuring the Mifeprex is dispensed only in certain healthcare settings by or under the supervision of a certified prescriber.
4. Removal of the Patient Agreement Form (ETASU D): I concur with the clinical review team that the Patient Agreement Form, which requires a patient's signature, does not add to safe use conditions for the patient for this REMS and is a burden for patients. It is standard of care for patients undergoing pregnancy termination to undergo extensive counseling and informed consent. The Patient Agreement Form contains duplicative information already provided by each healthcare provider or clinic. I believe that it is much more critical for the healthcare provider who orders or prescribes Mifeprex to provide and discuss informed consent derived from their own practice so that care can be individualized for the patient.

I support that the Mifeprex REMS with ETASUs A and C remain in place to support conditions critical to the use of the drug. Therefore, the implementation system and timetable for assessments should continue.

I also agree with the clinical review team that the reporting requirements should only be required for deaths. It is important that the Agency be informed of any deaths with Mifeprex to monitor new safety signals or trends. However, after 15 years of reporting serious adverse events, the safety profile for Mifeprex is essentially unchanged. Therefore, I agree that reporting of labeled serious adverse events other than deaths can be collected in the periodic safety update reports and annual reports to the Agency.

In summary, I believe that the benefit-risk profile for Mifeprex continues to be favorable and with the agreed-to labeling changes and REMS modifications, the Mifeprex REMS program will continue to assure safe use. Therefore, I support approval of this efficacy supplement and REMS modifications.

Addendum:

On March 28, 2016, Dr. Janet Woodcock, the Director, Center for Drug Evaluation and Research, asked (b) (6) and the (b) (6) (b) (6) to continue to include a Patient Agreement Form in the REMS for Mifeprex (see March 28, 2016 Memorandum from Janet Woodcock, MD, Director, Center for Drug Evaluation and Research, through the (b) (6) (b) (6)).

Therefore, the Patient Agreement Form will be retained and other changes will be made in the REMS to reflect that it is being retained.

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/s/

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(b) (6)

03/29/2016

# Exhibit 33

Beverly Winikoff, et al., *Extending Outpatient Medical Abortion Services Through 70 Days of Gestational Age*, 120 Obstetrics & Gynecology 1070 (2012)



# Extending Outpatient Medical Abortion Services Through 70 Days of Gestational Age

Beverly Winikoff, MD, MPH, Ilana G. Dzuba, MHS, Erica Chong, MPH, Alisa B. Goldberg, MD, MPH, E. Steve Lichtenberg, MD, MPH, Carol Ball, MD, Gillian Dean, MD, MPH, Daniel Sacks, MD, William A. Crowden, BA, and Yael Swica, MD, MPH

**OBJECTIVE:** To estimate the efficacy and acceptability of medical abortion at 64–70 days from last menstrual period (LMP) and to compare it with the already proven 57–63 days from LMP gestational age range.

**METHODS:** This prospective, comparative, open-label trial enrolled 729 women with pregnancies 57–70 days from LMP requesting abortion at six U.S. clinics. Medical abortions were managed with 200 mg mifepristone and 800 micrograms buccal misoprostol and sites' service delivery protocols. Follow-up visits occurred 7–14 days after mifepristone, with an abortion considered complete if surgical intervention was not performed. Success, ongoing pregnancy, and acceptability rates were compared.

**RESULTS:** A total of 629 cases were analyzable for efficacy. Success rates were similar in the two groups (57–63 days group: 93.5%, 95% confidence interval [CI] 90–96; 64–70 days group: 92.8%, 95% CI 89–95). Ongoing

pregnancy rates also did not differ significantly (57–63 days: 3.1%, 95% CI 1.6–5.8; 64–70 days: 3.0%, 95% CI 1.5–5.7). Acceptability was high and similar in both arms, with most women (57–63 days: 87.4%; 64–70 days: 88.3%) reporting that their experience was either very satisfactory or satisfactory.

**CONCLUSION:** Medical abortion with mifepristone and misoprostol in current outpatient settings is an efficacious and acceptable method of ending pregnancies 64–70 days from LMP and can be offered without alteration of existing services.

**CLINICAL TRIAL REGISTRATION:** ClinicalTrials.gov, www.clinicaltrials.gov, NCT00997347.

(*Obstet Gynecol* 2012;120:1070–76)

DOI: <http://10.1097/AOG.0b013e31826c315f>

**LEVEL OF EVIDENCE: II**

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*Presented at the National Abortion Federation's Annual Meeting, April 10–12, 2011, Chicago, Illinois, and at Reproductive Health 2010, September 25, 2010, Atlanta, Georgia.*

*The findings and conclusions in this article are those of the authors and do not necessarily represent the views of Planned Parenthood Federation of America.*

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## Financial Disclosure

*The authors did not report any potential conflicts of interest.*

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When medical abortion with mifepristone and misoprostol was approved by the U.S. Food and Drug Administration (FDA) in 2000, the regimen was recommended for outpatient use through 49 days from the last menstrual period (LMP).<sup>1</sup> Extensive research and more than 11 years of experience in the United States with approximately 1.75 million uses have established that medical abortion is safe and effective through 63 days from LMP when used by women at home (May 2011, Danco Laboratories, personal communication).<sup>2–6</sup>

Generally, women in the United States whose first-trimester pregnancies are beyond 63 days from LMP are not offered medical abortion with mifepristone and misoprostol. Medical abortion after 63 days from LMP is occasionally available outside the United States, but only on an inpatient basis using complex regimens.<sup>7–9</sup> Inpatient protocols typically involve re-dosing of medications, vaginal speculum examination, and an overnight stay, and are burdensome for women, providers, and health care systems. Data supporting use of medical abortion past 63 days from

LMP in outpatient services are limited to one small trial, but results were not available when this study began.<sup>10</sup> Our study sought to estimate the efficacy and acceptability of the most common outpatient medical abortion regimen in the United States (200 mg mifepristone and 800 micrograms buccal misoprostol) through 70 days from LMP and to compare outcomes between women with pregnancies of 64–70 days' duration and women with pregnancies in the range of 57–63 days. The gestational age limit of 70 days extends the usual gestational age cutoff of 63 days by 1 week.

## MATERIALS AND METHODS

The study was performed at six facilities: Family Planning Associates Medical Group (Chicago, IL), Planned Parenthood League of Massachusetts (Boston, MA), Planned Parenthood of New York City (New York, NY), Planned Parenthood of Waco (Waco, TX), Presidential Women's Center (West Palm Beach, FL), and Planned Parenthood of Minnesota, North Dakota, South Dakota (St. Paul, MN). The Quorum Review Institutional Review Board approved the protocol.

Women seeking pregnancy termination were invited to participate in the study if they were eligible for medical abortion, were at least 18 years old, and had a confirmed intrauterine pregnancy 57 through 70 days from LMP, based on routine ultrasound practices of the respective study sites (crown-rump length+42 was most commonly used). Participants had to be willing and able to provide informed consent, have access to a telephone and emergency transportation, be able to speak and read English or Spanish, and agree to follow study protocols. Screening and enrollment generally occurred during the same visit, except when a state-mandated 24-hour waiting period after informed consent required a second visit.

On day 1, participants swallowed mifepristone 200 mg (Mifeprex) in the clinic and then were provided with misoprostol 800 micrograms to take 24–48 hours later at home. Women were instructed to hold the misoprostol buccally for 30 minutes before swallowing any remains. Analgesics and anti-nausea medications were dispensed or prescribed according to local standards at each facility, and participants were counseled to call the clinic with questions or concerns. Participants maintained a diary for up to 15 days to record time of misoprostol administration, bleeding, expulsion time (if recognized), pain medications used, and days of missed work or school.

Participants returned to the study site 7 to 14 days after using mifepristone (according to clinic practice) for clinical assessment, which included ultrasonography. Uterine suction curettage was recommended for women with ongoing pregnancies. Women with nonviable pregnancies (eg, empty sac or static size with absent cardiac activity on ultrasonography) could opt for suction curettage, expectant management, or a second misoprostol dose. If either of the latter two options was chosen, then women were asked to return to the clinic in 1 week for further follow-up. If a persistent nonviable pregnancy was diagnosed at the extended follow-up visit, suction curettage was recommended. Providers also intervened surgically if they deemed it medically necessary or at the patient's request. After expulsion of uterine contents was confirmed, women responded to a semi-structured interview about their experiences with the medical abortion overall, the incidence of side effects and their severity (based on their own definitions of mild, moderate, and severe), and the acceptability of the procedure. If a participant failed to return for a follow-up visit, then assessment of abortion status and the interview could be conducted by telephone. Study sites were required to document at least three attempts to contact women who were lost to follow-up.

The study's primary objective was to assure that an outpatient medical abortion regimen could be used in gestations 64–70 days from LMP and achieve a success rate of at least 90%, which would characterize a clinically acceptable regimen. A cohort of women with gestations 57–63 days from LMP was also enrolled to serve as a comparison; 334 women per group were needed to detect a 5% or greater lower efficacy than the hypothesized 95% success rate in the 57–63 days group, based on previously published reports ( $\alpha=0.05$ ,  $1-\beta=0.8$ , using a one-tailed test) and would allow us to estimate a success rate of 90% with a confidence interval (CI) of  $\pm 3.2\%$ .<sup>2–3,11</sup> Data were analyzed using SPSS 15.0. An independent data and safety monitoring committee reviewed the interim results for safety and efficacy after 50% of the data were available.

The primary outcome of the trial was complete abortion without surgical intervention at any point, regardless of the number of misoprostol doses used. Secondary outcomes included side effects, patient satisfaction and acceptability, days of heavy bleeding, days of missed work or school, and number of calls and unscheduled visits to the clinic. One-tailed  $P<.05$  was considered to indicate statistical significance. We chose to use one-tailed  $P$  values because our objective was to determine whether use of medical abortion in

the gestational age range of 64–70 days would result in worse outcomes than its current use in the 57- to 63-day age range. Binomial proportion CIs for efficacy rates were calculated. We used Fisher's exact test to determine differences in proportions, and for continuous variables we used the Student *t* test to determine differences in means.

## RESULTS

Between August 2009 and February 2011, the study sites enrolled 729 women; 379 women in the 57–63 days group and 350 women in the 64–70 days group. Fifty-three (14%) women in the earlier and 45 (13%) in the later gestational age group were lost to follow-up, and two women, one from each group, withdrew before using mifepristone. Enrollment was continued to 729 women to compensate for loss to follow-up. Six-hundred twenty-nine cases had outcome data, short of the estimated sample size of 668. Analysis of the outcomes at that time were conducted to determine the utility of continuing the study and whether a statistically significant difference in success would be possible if the study were to continue and the remaining 39 analyzable case records were available. We analyzed the hypothetical scenario that maximized the possible difference in efficacy between the two groups by adding all 39 hypothetical additional cases to the 57–63 days group (because it had the higher efficacy rate) and assuming that every woman had a successful abortion (to model the maximum mathematical differences possible between the groups). This model improved the efficacy rate in the 57–63 days study group by 0.7 percentage points and doubled the difference in efficacy between the two gestational age groups from 0.7% to 1.4%. Comparing the projected success rates of the two gestational age groups resulted in  $P=0.2$ . It was therefore determined that enrolling all 688 women would not show a statistically significant or a clinically meaningful difference in success

rates. The study would have required an additional 13,120 women with follow-up in each study group (total 26,240 analyzable cases) to be able to find a statistically significant difference between the observed success rates. Therefore, a total of 629 medical abortions, 325 in the 57–63 days group and 304 in the 64–70 days group, were analyzed for efficacy in the final analysis. Baseline characteristics of women in the two groups were similar for mean age, education level, gravidity, and previous abortions (Table 1).

Efficacy of the outpatient medical abortion regimen in the 57–63 days group was 93.5% (95% CI 90.1–95.9) and 92.8% (95% CI 89.1–95.3;  $P=.41$ ) in the 64–70 days group (Table 2). Three percent of women in both groups had a surgical intervention because of ongoing pregnancy (57–63 days: 3.1%, 95% CI 1.6–5.8; 64–70 days: 3.0%, 95% CI 1.5–5.7;  $P=.62$ ). Rates of surgical intervention attributable to persistent nonviable pregnancy or sac ( $P=.33$ ), substantial uterine debris ( $P=.29$ ), excessive prolonged bleeding ( $P=.75$ ), or woman's request ( $P=.86$ ) were comparable between study groups. There was no significant difference in efficacy by study site ( $P=.137$ ).

Approximately 5.2% of women in the 57–63 days group and 5.3% of women in the 64–70 days group had incomplete abortion diagnosed (ie, persistent gestational sac or substantial debris) at their first follow-up visits ( $P=.56$ ). The majority were treated with a second dose of misoprostol, with those in the 57–63 days group receiving a second dose at a higher rate than those in the 64–70 days group (76.5% compared with 56.3%;  $P=.195$ ). Of those who received a second dose of misoprostol and underwent an extended follow-up evaluation, 91% (10 of 11) in the earlier and 66.7% (6 of 9) in the later gestational age group were determined to have a complete abortion ( $P=.974$ ).

Almost 70% of participants in each group reported a time of expulsion at follow-up. Among women who reported a time of expulsion, those in

**Table 1. Participant Demographic Characteristics**

	57–63 d (n=325)	64–70 d (n=304)	<i>P</i> (Two-Tailed)
Age (y)	26 (18–42)	26 (18–42)	.66
Primigravida woman	32 (103)	31 (94)	.86
Previous abortion	47 (154)	48 (146)	.87
Previous medical abortion	21 (67)	24 (72)	.39
Education level	322	303	4 unknowns
Less than high school	8 (24)	9 (26)	.71
High school	59 (191)	60 (183)	.85
University	27 (87)	27 (83)	.99
Postgraduate	6 (20)	4 (11)	.19

Data are mean (range), n (%), or n unless otherwise specified.

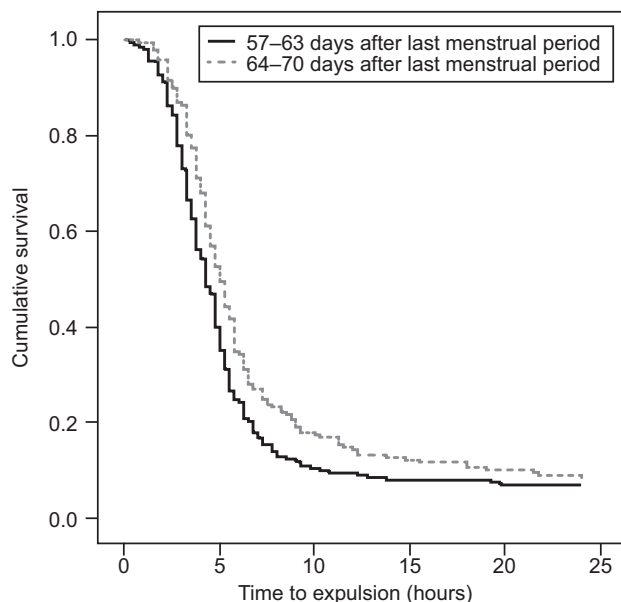


**Table 2. Efficacy and Major Adverse Events by Gestational Age Group**

	57–63 d (n=325)	64–70 d (n=304)	P (One-Sided)
Success	93.5 (304; 90–96)	92.8 (282; 89–95)	.41
Interventions	6.5 (21)	7.2 (22)	
Ongoing pregnancies	3.1 (10)	3.0 (9)	.62
Persistent nonviable sac	0.92 (3)	1.6 (5)	.33
Substantial debris in uterus	0.31 (1)	1.0 (3)	.29
Excessive prolonged bleeding	1.2 (4)	1.0 (3)	.75
Woman's request	0.61 (2)	0.33 (1)	.86
Other	0.31 (1)	0.33 (1)	.73
Major adverse events			
Went to emergency department	3.7 (12)	4.6 (14)	.36
Received blood transfusion	0.6 (2)	0.3 (1)	.52
Admitted to hospital	0.9 (3)	0.7 (2)	.53

Data are % (n; 95% confidence interval) or % (n) unless otherwise specified.

the earlier gestational age group were significantly more likely than those in the later gestational age group to expel sooner (Fig. 1; log-rank test  $P=.005$ ). This difference in reported expulsion time was most notably seen at 3 hours after using misoprostol (37.7% in week 9 compared with 22.5% in week 10;  $P=.001$ ), but equal numbers (93.1% compared with 92.1%, respectively;  $P=.43$ ) reported expulsion by 24 hours (Fig. 1).



**Fig. 1.** Time from misoprostol administration to pregnancy expulsion. Survival curves of the number of hours since misoprostol administration until pregnancy expulsion for women 57–63 days from last menstrual period or 64–70 days from last menstrual period. Includes women who reported a time of expulsion, excluding those with ongoing pregnancies or persistent nonviable sac at follow-up. Log-rank test  $P=.005$ .

Winikoff. Medical Abortion Through 70 Days From LMP. *Obstet Gynecol* 2012.

Twenty-nine women made visits to an emergency department, primarily for pain and bleeding during the study period (3.7% from the earlier gestational age group and 4.6% from the later group ( $P=.35$ )) (Table 2). Three women received blood transfusions, two in the 57–63 days group and one in the 64–70 days group ( $P=.52$ ). One woman in the 57–63 days group was admitted to the hospital and was successfully treated for *Escherichia coli* sepsis, and one woman in the 57–63 days group with a history of chronic pancreatitis was admitted to the hospital for recurrence of her disease.

Eighty-five percent of participants completed and submitted the diaries they maintained for up to 15 days. Mean duration of heavy bleeding did not differ significantly by group (Table 3). There was no significant difference in mean days of work or school missed by women because of the abortion (1.85 in 57–63 days group compared with 1.80 in 64–70 days group;  $P=.81$ ).

The side effect profiles of each study group were similar, with no significant differences except for vomiting (Table 3). A minority of women in each group experienced this side effect, but fewer in the earlier gestational age group (36% compared with 46%;  $P=.01$ ). However, severe vomiting was no different in the two groups (10.7% for 57–63 days compared with 12.0% for 64–70 days;  $P=.35$ ). Opiates were reportedly used more often for pain relief by women in the 64–70 days group (76% in the 57–63 days group compared with 84%;  $P=.003$ ), but nonsteroidal anti-inflammatory drug use did not differ. Mean days of any analgesic use were the same in both groups. Fewer women in the 57–63 days group reported use of antiemetic medication (34% compared with 46%;  $P=.002$ ). The study participants requested relatively little clinic staff time beyond the scheduled study visits. Only 20%

**Table 3. Side Effect and Bleeding Profile**

Side Effects	57–63 d (n=318)	64–70 d (n=300)	P (One-Sided)
None	22.6 (72)	17.0 (51)	.05
Chills	24.2 (77)	22.7 (68)	.36
Fever	11.9 (38)	10.3 (31)	.31
Vomiting	35.8 (114)	45.7 (137)	.008
Nausea	50.0 (159)	51.7 (155)	.37
Diarrhea	17.9 (57)	17.3 (52)	.47
Heavy bleeding	319	298	
Days of heavy bleeding	2.5±2.06 (0–14)	2.3±1.86 (0–11)	.09
Median days of heavy bleeding	2	2	

Data are % (n), n, or mean±standard deviation (range) unless otherwise specified.

of women in both groups made phone calls because of concerns related to their abortion, and 4% of women in the earlier and 3% of women in the later gestational age groups made unanticipated clinic visits.

The majority of women in both groups (57–63 days: 87.4%; 64–70 days: 88.3%) reported being either satisfied or very satisfied with the medical abortion method, and 78% and 79% of women in the two groups, respectively, reported that they would choose medical abortion again instead of surgery. Women in the earlier gestational age group were as likely to report seeing the pregnancy or some part of it as those in the later gestational age group (64% compared with 69.3%;  $P=.10$ ). There were no significant differences in women's reported reactions to what they saw, with the exception that women in the earlier gestational age group were more likely to report "nothing or no feeling" (13.9% compared with 8.2%;  $P=.04$ ) and those in the later group were more likely to report that they were "relieved" (7.4% compared with 13.9%;  $P=.02$ ).

## DISCUSSION

The results show that medical abortion with an outpatient regimen of 200 mg mifepristone followed 24 to 48 hours later by 800 micrograms buccal misoprostol self-administered at home is efficacious and acceptable in women 64 to 70 days from LMP and is not statistically or clinically different from a current outpatient medical abortion protocol used with women 57–63 days from LMP. In 2000, the FDA approved mifepristone based on an efficacy of 92% for gestations up to 49 days from LMP.<sup>12</sup> The success rate achieved in this study during week 10 of gestation (92.8%) is similar to that rate and clinically acceptable. Based on this evidence, medical abortion using the study protocol can be extended from 63 days from LMP to 70 days from LMP without reconfiguration of existing outpatient clinical services. Our findings are consistent with those of Boersma et al,<sup>10</sup> who

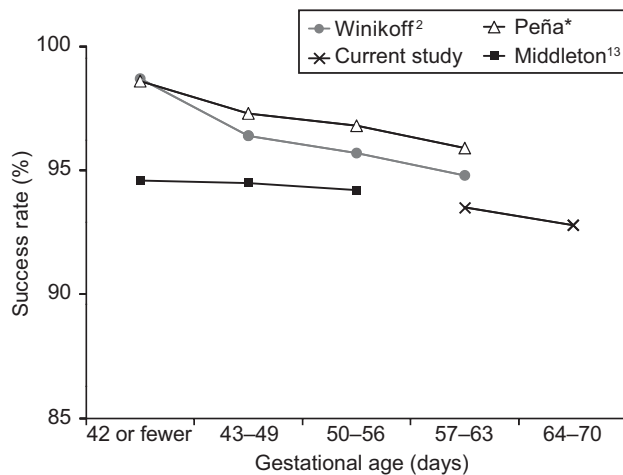
offered the same outpatient medical abortion regimen as in the current study to 26 women with gestational ages 64–70 days from LMP, but with an interval of 24–36 hours between the mifepristone and misoprostol doses. That study found 96% success in those women but was too small to provide reliable point estimates of success rates.

The study cannot reject the null hypothesis that there is no difference between the success rates of medical abortion among women with pregnancies of 9 and 10 weeks of gestation. Although the inability to reject the null hypothesis theoretically could be attributable to early cessation of the study, the observed differences between study groups are much smaller than those originally hypothesized and are not clinically meaningful. The additional analyses conducted also suggest that continuing enrollment to include 668 analyzable cases would not have affected the study conclusions.

The overall high efficacy of the medical abortion regimen used in this study through 63 days from LMP is well-documented, and only a very minimal decline in efficacy as gestational age increases has been noted.<sup>2,13</sup> The trend observed in the two point estimates for success in weeks 9 and 10 in this study is consistent with such a small decline (Fig. 2), alleviating concern of an abrupt decline in efficacy of the method beyond 63 days from LMP.

The study was not powered to detect a difference in safety outcomes because major adverse events attributable to medical abortion (eg, hospitalizations, emergency department visits, and blood transfusions) are rare. No medical abortion studies (including the pilot studies on which FDA approval was based) were powered to detect rates of rare occurrences such as transfusion or hospitalization. Similar to those studies, the occurrence of major adverse events in this study was very infrequent.

Many studies have explored women's experiences with outpatient medical abortion in the first trimester,<sup>14</sup>



**Fig. 2.** Efficacy of mifepristone medical abortion with 800 micrograms buccal misoprostol from 49 to 70 days from last menstrual period. Illustration of success rates by gestational age from different studies that used the same medical abortion regimen as in this study. \*Peña M. Medicamentos para la interrupción legal del embarazo: La experiencia de la Secretaría de Salud del Distrito Federal (Mexico). 20th Congress of the Latin American Federation of Obstetrics and Gynecology (FLASOG) 2011; Managua, Nicaragua.

Winikoff. Medical Abortion Through 70 Days From LMP. *Obstet Gynecol* 2012.

but often the information is not disaggregated by week. Although our findings do not show any differences between the two study groups in such aspects as bleeding profiles, days of school or work missed, and reports of seeing the expulsion, women's experiences at these later weeks of gestational age may differ in some ways from women with earlier first-trimester pregnancies. The results from this study may help clinicians who provide medical abortion to women with pregnancies 57–70 days of gestational age to tailor counseling messages to prepare women for what to expect. For example, more than two-thirds of women reported witnessing uterine expulsion, so women should be counseled on that likelihood. Women with gestations in week 10 may expel their pregnancies less quickly after using misoprostol, but perhaps this is not surprising given the slightly larger size of the gestational sac at the later gestational age. The fact that more women in week 10 expressed relief after their medical abortions could be an artifact of participating in the test group of a research trial.

Some women may have been misclassified into study groups based on usual variability in gestational age dating by ultrasonography. To be sure that such misclassification would not have affected study results, reanalysis of success among women with pregnancies at the opposite extremes of the gestational age

spectrum considered in this study (ie, a comparison of the earlier half of the early age range with the latter half of the later age range), as well as by standardizing gestational age assessment, did not affect our outcomes or our conclusions (data not shown).

The content of counseling was not dictated by the study protocol and was based on usual counseling provided. Possible assumptions that pain, bleeding, and the size of the expelled fetus in week 10 may be more than at earlier weeks of gestation could have had an effect on women's perceptions. It is also possible that there were slight differences in counseling messages as a result of the counselors' knowledge of gestational age in each woman. Similarly, observations and experience amassed during the course of the study may have resulted in adjustments in counseling messages to later enrollees, better-preparing women with pregnancies in week 10 for what they might experience.

The study sites already were highly experienced at providing medical abortion and were accustomed to administering the specific regimen used in this study. Therefore, the observed efficacy rates may not be generalizable to clinics that are less experienced. Results also are not generalizable to regimens other than the one studied, for either efficacy or the side effects of misoprostol, which are known to vary by route and dose. Last, because adverse events were so rare in our study, the sample size was not sufficient to characterize adequately the occurrence of adverse events for women who terminate their pregnancies medically during the ninth or tenth week other than to say that serious events are infrequent and side effects are tolerable.

In conclusion, the regimen of 200 mg mifepristone and 800 micrograms buccal misoprostol is efficacious and acceptable for women seeking medical abortion with pregnancies of 70 days or less. The findings of this research are important for expanding the availability of this nonsurgical option to women seeking termination of pregnancy in the first trimester.

## REFERENCES

1. United States Food and Drug Administration. Approval letter MIFEPREX<sup>TM</sup> (mifepristone) tablets. Available at: [http://www.accessdata.fda.gov/drugsatfda\\_docs/applletter/2000/20687\\_appltr.htm](http://www.accessdata.fda.gov/drugsatfda_docs/applletter/2000/20687_appltr.htm). Retrieved September 22, 2011.
2. Winikoff B, Dzuba IG, Creinin MD, Crowden WA, Goldberg AB, Gonzales J, et al. Two distinct oral routes of misoprostol in mifepristone medical abortion: a randomized controlled trial. *Obstet Gynecol* 2008;112:1303–10.
3. von Hertzen H, Huong NT, Piaggio G, Bayalag M, Cabezas E, Fang AH, et al. Misoprostol dose and route after mifepristone for early medical abortion: a randomised controlled noninferiority trial. *BJOG* 2010;117:1186–96.
4. Creinin MD, Fox MC, Teal S, Chen A, Schaff EA, Meyn LA, et al. A randomized comparison of misoprostol 6 to 8 hours

- versus 24 hours after mifepristone for abortion. *Obstet Gynecol* 2004;103:851–9.
5. Schaff EA, Fielding SL, Westhoff C, Ellertson C, Eisinger SH, Stadalius LS, et al. Vaginal misoprostol administered 1, 2, or 3 days after mifepristone for early medical abortion: A randomized trial. *JAMA* 2000;284:1948–53.
  6. Jones RK, Kooistra K. Abortion incidence and access to services in the United States, 2008. *Perspect Sex Reprod Health*. 2011;43:41–50.
  7. Ashok PW, Flett GM, Templeton A. Termination of pregnancy at 9–13 weeks' amenorrhea with mifepristone and misoprostol. *Lancet* 1998;352:542–3.
  8. Hamoda H, Ashok PW, Flett GM, Templeton A. Medical abortion at 9–13 weeks' gestation: a review of 1076 consecutive cases. *Contraception* 2005;71:327–32.
  9. Løkeland M, Iversen OE, Dahle GS, Nappen MH, Ertzeid L, Bjørge L. Medical abortion at 63 to 90 days of gestation. *Obstet Gynecol* 2010;115:962–8.
  10. Boersma AA, Meyboom-de Jong B, Kleiverda G. Mifepristone followed by home administration of buccal misoprostol for medical abortion up to 70 days of amenorrhoea in a general practice in Curacao. *Eur J Contracept Reprod Health Care* 2011;16:61–6.
  11. Cohen J. *Statistical power analysis for the social sciences*. 2nd ed. Hillsdale (NJ): Lawrence Erlbaum Associates; 1988. p. 179–214.
  12. Spitz IM, Bardin CW, Benton L, Robbins A. Early pregnancy termination with mifepristone and misoprostol in the United States. *N Engl J Med* 1998;338:1241–7.
  13. Middleton T, Schaff E, Fielding SL, Scahill M, Shannon C, Westheimer E, et al. Randomized trial of mifepristone and buccal or vaginal misoprostol for abortion through 56 days of last menstrual period. *Contraception* 2005;72:328–32.
  14. Swica Y, Raghavan S, Bracken H, Dabash R, Winikoff B. Review of the literature on patient satisfaction with early medical abortion using mifepristone and misoprostol. *Expert Rev Obstet Gynecol* 2011;6:451–68.



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## Original research article

# Efficacy and safety of medical abortion using mifepristone and buccal misoprostol through 63 days<sup>☆,☆☆</sup>

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## Abstract

**Objective:** The aim of this study was to report on the safety and efficacy of an evidence-based medical abortion regimen utilizing 200 mg of mifepristone orally followed by home use of 800 mcg misoprostol buccally 24–48 h later through 63 days estimated gestational age.

**Study design:** We analyzed outcomes in women presenting for medical abortion between April 1, 2006, and May 31, 2011, using an evidence-based alternative to the United States Food and Drug Administration (FDA)-approved regimen. Cases were identified for this descriptive study from our electronic practice management (EPM) database, and our electronic database on adverse events was queried for information on efficacy and safety. The primary outcome was successful abortion. Logistic regression was used to identify predictors of successful abortion.

**Results:** Among the 13,373 women who completed follow-up, efficacy of the regimen was 97.7%. Efficacy was highest at 29 to 35 days (98.8%) and 36 to 42 days (98.8%) of gestation and lowest at 57 to 63 days (95.5%). The odds of needing aspiration for any reason were greatest at higher gestational ages. Rates of infection requiring hospitalization and rates of transfusion were 0.01 and 0.03%, respectively.

**Conclusions:** An evidence-based regimen of 200 mg of mifepristone orally followed by home use of 800 mcg of buccal misoprostol 24–48 h later is safe and effective through 63 days estimated gestational age. Further, the need for aspiration for any reason was low, and hospitalization was rare.

**Implications:** This study reinforces the safety and efficacy of the evidence-based regimen for medical abortion (200 mg mifepristone orally followed by home use of 800 mcg of misoprostol buccally 24–48 h later) through 63 days estimated gestational age, and contributes to the existing evidence against restrictions requiring use of the FDA-approved regimen.

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**Keywords:** Medical abortion; Mifepristone; First-trimester abortion; Evidence-based regimen; Buccal misoprostol; Efficacy

## 1. Introduction

The United States Food and Drug Administration (FDA) approved the use of mifepristone and misoprostol for pregnancy termination in 2000. The regimen, labeled for use through 49 days estimated gestational age, required a minimum

of three visits to the healthcare provider. Six hundred milligrams of mifepristone was taken orally at Visit 1, followed in 2 days by misoprostol 400 mcg, also taken orally. A third follow-up visit was required in 14 days to ensure that the abortion was complete. The efficacy of this regimen ranged from 92 to 97% [1–3]. Publications soon followed providing an evidence base for alterations to the regimen. Alterations included a lower dose of mifepristone, different routes of administration of misoprostol, variations in the timing of misoprostol administration, home use of misoprostol, and increasing the gestational age limit for the regimen [4–11]. A recent publication confirmed the low rate of significant adverse events with use of the evidence-based regimen [11].

In 2008, a prospective study was published describing the use of 200 mg of mifepristone followed in 24 to 36 h by 800 mcg of buccal misoprostol for pregnancy termination to 63

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days of gestation with a success rate for the regimen of 96.2% [8]. Despite the growing literature supporting evidence-based provision of medical abortion, some providers are required by law to limit the provision of medical abortion to that regimen, which was FDA-approved more than a decade ago [12]. The goal of the current study was to assess, in a much larger cohort of patients, the safety and efficacy of an evidence-based medical abortion regimen utilizing 200 mg of mifepristone orally followed by home use of 800 mcg of misoprostol buccally 24–48 h later through 63 days estimated gestational age.

## 2. Materials and methods

### 2.1. Medical abortion protocols and monitoring

Our large network of urban healthcare centers includes 19 health centers providing approximately 15,000 abortions per year, of which about 30% are medical abortions. Demographic information, treatment dates, and diagnostic codes for all patients were retrieved using the electronic practice management (EPM) billing system. Some clinical information was retrieved from an electronic medical records (EMR) system, which was gradually implemented across all study sites between 2008 and 2010. All patients undergo an ultrasound examination for pregnancy dating prior to abortion. The clinician administering the medication abortion performed and interpreted the ultrasound. All clinicians had undergone the same standardized training and were monitored regularly to ensure accuracy and to maintain consistency. Ultrasound machines using a Hadlock scale calculated gestational age in days; herein, we analyze and report gestational age in 7-day increments (e.g., 22 to 28 days). Since April 2006, our medical abortion regimen has consisted of 200 mg of mifepristone taken orally at the health center followed by 800 mcg of buccal misoprostol used by the patient at home 24 to 48 h later. Medical protocols during the study period allowed for repeat doses of misoprostol for patients who had an incomplete medical abortion. Data on which patients received a repeat dose are not available from the EPM system, but only in the EMR system; therefore, for patients seen at sites that had not yet implemented EMR at the time of treatment, information on whether a repeat dose of misoprostol was given is not available. For the first 3 years of the study period, the upper gestational age limit for this regimen was 56 days. In February 2009, based on newly published data, the upper limit was increased to 63 days [8]. All patients were scheduled to return in 7 to 14 days for a postabortion evaluation. Beginning in 2007, all patients also received routine antibiotic coverage beginning on the day of the mifepristone administration. The standard antibiotic regimen was a 7-day course of doxycycline (100 mg twice a day), with an alternative regimen of one dose of azithromycin (1 g) for cases in which doxycycline was contraindicated.

Our EPM database contains information on all patients undergoing medical abortion, including patient demographics and the ultrasound-determined gestational age.

We also maintain a separate electronic database of adverse events including ongoing pregnancy, aspiration for symptoms and/or retained products of conception, infection requiring hospitalization, and hemorrhage requiring transfusion.

### 2.2. Statistical methods

Bivariate and multivariate logistic regression were used to assess predictors of successful medical abortion. Covariates available in our data set were poverty level, race/ethnicity, gestational age, and patient age; other patient-level data were not available. Results were considered statistically significant at  $p < .05$ . Statistical analysis was performed using Stata/SE 11.2 (College Station, TX).

The primary outcome of interest was successful abortion. A successful abortion was defined as expulsion of the pregnancy without the need for aspiration. Patients who required aspiration for an ongoing pregnancy or symptoms such as pain or bleeding were considered to have had unsuccessful medical abortions. We queried our adverse events database to identify continuing pregnancies (those pregnancies with documented fetal growth or cardiac activity seen at the follow-up), all cases of aspiration, and hospitalization for either infection or transfusion. We cross-checked this against the list of postprocedure visits in our EPM system in order to ensure that all cases had been identified.

Institutional review board (IRB) approval was obtained from the Ethical and Independent Review Service of Independence, MO, and an exemption for analysis of the existing data was granted by the Princeton University IRB.

## 3. Results

### 3.1. Sample description

For this descriptive study, we queried our EPM database and identified 15,890 patients who had a medical abortion between April 1, 2006, and May 31, 2011. During the period under review, medical abortions were provided at 14 different clinic sites belonging to our network in one urban area, all using the same evidence-based protocol. There were 2470 (15.5%) patients who failed to return for a follow-up visit and were excluded from analysis. An additional 20 patients were excluded from the analysis due to missing data on gestational age, and a further 27 patients were excluded because they did not complete the medical abortion (these patients either changed their mind and chose a surgical abortion, were ineligible for a medical abortion because they were beyond the 63-day gestational limit, or began the regimen but did not take all of the medications). This left 13,373 patients for analysis.

Demographic characteristics of the 13,373 women who had a medical abortion between April 1, 2006, and May 31, 2011, and who returned for follow-up are shown in Table 1. Half of the women were between the ages of 18 and 24, and small proportions were under the age of 18 (4.5%) or 40 or

Table 1

Demographic characteristics of women having a medical abortion with mifepristone 200 mg and misoprostol 800 mcg buccally (N=13,373)

	n	%
Gestational age (days)		
22–28	554	4.1
29–35	1080	8.1
36–42	2495	18.7
43–49	4816	36.0
50–56	3142	23.5
57–63	1286	9.6
Poverty level (% FPL)		
0–100	9679	72.4
>100	3694	27.6
Race/ethnicity		
Hispanic/Latino	6215	46.5
White	3235	24.2
African American	1263	9.5
Asian	1172	8.8
Other/declined	1487	11.1
Patient age (years)		
<18	605	4.5
18–24	6684	50.0
25–29	3317	24.8
30–34	1613	12.1
35–39	855	6.4
40+	299	2.2

older (2.2%). Nearly half of women identified as Hispanic or Latino, and 72% reported an income at or below the poverty line. The most frequent gestational age in our data set was 43 to 49 days (36.0%), and the least frequent was 22 to 28 days (4.1%).

### 3.2. Frequency and predictors of successful abortion

Termination of pregnancy with 200 mg of oral mifepristone followed by 800 mcg of buccal misoprostol 24–48 h later was successful among 97.7% of women who completed follow-up. Only 307 (2.3%) of the 13,373 women included in this study underwent aspiration for any reason. Specifically, 70 (0.5%) women had a continuing pregnancy, and 237 (1.8%) women required aspiration for reasons other than continuing pregnancy, most commonly due to reported symptoms of pain and/or bleeding. Data on the need for a repeat dose of misoprostol were available from a subset of women from clinics in which the EMR system was used, which included 7335 women (54.8% of the total sample). Of these 7335 women, 87 (1.2%) received a repeat dose of misoprostol.

Table 2 shows the proportion of patients requiring aspiration for ongoing pregnancy or for symptoms, such as heavy bleeding, by gestational age. The proportion with ongoing pregnancy ranged from 0.15% for those at 36 to 42 days of gestation to 1.63% at 57 to 63 days of gestation. Compared with the reference category (43 to 49 days), odds of ongoing pregnancy were greater for those at the highest gestational age. The proportion of women treated with aspiration for symptoms, not ongoing pregnancy, ranged from 0.65 to 2.49%. The incidence of hospitalization for

infection or hemorrhage requiring transfusion was very low (Table 3). In total, six women required hospitalization for any reason (two women were hospitalized for infection, and four were hospitalized for transfusion), and incidence was at or below 0.1% among all gestational ages.

In a multivariate logistic regression model (Table 4), poverty level and race/ethnicity were not significant predictors of successful abortion. Certain categories of gestational age were significantly associated with success; compared with the reference category (43 to 49 days), those at 36 to 42 days of gestation had greater odds of success, whereas those at 50 to 56 days and 57 to 63 days had lower odds of success. Compared with the reference category (18 to 24), those in the middle three age groups had significantly lower odds of success, but differences for those in the youngest (17 and under) and highest (40 and older) age groups were not significant.

### 3.3. Loss to follow-up

A comparison of patients who completed follow-up and those who were lost to follow-up is presented in Table 5. Compared with patients at 43 to 49 days of gestation, patients at higher gestational ages were more likely to be lost to follow-up. For patients with incomes at or below the Federal Poverty Level (FPL), the odds of being lost to follow-up were greater than those above FPL. Odds of being lost to follow-up were greater for those younger than 18 (compared with those 18 to 24) and lower for those aged 40 and older.

## 4. Discussion

### 4.1. General implications

This study demonstrates that the evidence-based regimen for medical abortion (mifepristone 200 mg orally followed by home use of misoprostol 800 mcg buccally 24–48 h later) is highly effective through 63 days estimated gestational age, with an overall success rate of 97.7%. This is higher than the efficacy rates reported in two pivotal trials used in submission for FDA approval of mifepristone,[1,2] yet utilizes one-third the dose of mifepristone (200 mg rather than 600 mg) and buccal administration and home use of misoprostol rather than oral administration in the clinic. Repeat dosing of misoprostol was administered in only 1.2% of patients for whom this information is available, and given the way in which the EMR system was implemented across study sites, we can assume that this rate would be representative of the entire sample. Although efficacy is lower at later gestational ages, even in the 57- to 63-day range, this evidence-based regimen was still more effective than rates reported in the FDA-approved regimen, which sets the upper gestational age limit at 49 days. Furthermore, the rates of unsuccessful abortion in this study are lower than the rates reported in the two trials that were initially submitted to the FDA for approval of mifepristone.

Table 2

Aspiration for ongoing pregnancy, symptoms or any indication among those who completed follow-up, by gestational age.

Gestational age	Aspiration for ongoing pregnancy n (%)	OR	95% CI	Aspiration for symptoms n (%)	OR	95% CI	Aspiration for any reason *	OR	95% CI
22–28 days	4 (0.72)	2.69	0.87–8.27	11 (1.99)	1.39	0.73–2.65	15 (2.71)	1.39	0.80–2.43
29–35 days	5 (0.46)	1.72	0.61–4.83	7 (0.65)	0.45	0.21–0.98	13 (1.20)	0.61	0.34–1.10
36–42 days	4 (0.16)	0.59	0.19–1.82	25 (1.00)	0.70	0.44–1.10	30 (1.20)	0.61	0.40–0.92
43–49 days	13 (0.27)	ref		69 (1.43)	ref		94 (1.95)	ref	
50–56 days	23 (0.73)	2.72	1.38–5.39	64 (2.04)	1.43	1.01–2.02	97 (3.09)	1.60	1.20–2.13
57–63 days	21 (1.63)	6.13	3.06–12.28	32 (2.49)	1.76	1.15–2.80	58 (4.51)	2.37	1.70–3.31
Totals	70 (0.5)			237 (1.8)			307 (2.3)		

OR: odds ratio; CI: confidence interval

\* This column includes 29 cases wherein reason for aspiration is unknown.

This study adds to the growing literature supporting provision of medical abortion using evidence-based regimens, and supports the conclusion that legislative efforts to restrict medical abortion to the FDA regimen are based on political goals to restrict abortion services, not efficacy or patient safety.

#### 4.2. Limitations

Our study has some limitations. It is retrospective in nature and relies on the accuracy of our EPM database. However, review of our EPM system has shown a high degree of accuracy when compared with patient records [13]. In addition, we are not a closed system, and it is possible and even likely that some patients who experienced complications did not return to us for care. However, since many patients need to pay for aftercare obtained outside our system, but not within our system, it is more likely than not that the patients who did not return for follow-up did so because they did not feel that they needed follow-up, rather than that they were experiencing a complication. In that case, excluding them from our analysis would have tended to overestimate, rather than underestimate, the need for aspiration in our population. We based our analysis of efficacy only on those patients who did return for a follow-up visit, so we cannot exclude the possibility of additional visits or treatment elsewhere.

Loss to follow-up is common in studies of medical abortion, as many patients may determine on their own that their abortion is complete and that follow-up is not needed. The rate of loss to follow-up in this study (15.5%) is lower than loss to follow-up found in other clinical medical abortion studies, which report

loss of follow-up of 18 to 45% [14–17]. We found that loss to follow-up was significantly more common among those at higher gestational ages; given that odds of success are lower among those with more advanced pregnancies, it is possible that this study underestimates the true odds of unsuccessful abortion. Loss to follow-up was significantly higher among the youngest age group and lower among the oldest age group, but as these age categories were unrelated to whether the abortion was successful, we do not believe that these differences would systematically bias our results.

#### 4.3. Conclusion

In summary, an evidence-based regimen of mifepristone 200 mg orally followed by misoprostol 800 mcg buccally

Table 4

Factors associated with successful medical abortion in women using mifepristone 200 mg and misoprostol 800 mcg buccally (N=13,373)

	Successful n (%)	Unsuccessful n (%)	OR	95% CI
Gestational age (days)				
22–28	539 (97.3)	15 (2.7)	0.72	0.41–1.25
29–35	1067 (98.8)	13 (1.2)	1.68	0.94–3.01
36–42	2465 (98.8)	30 (1.2)	1.65	1.09–2.50
43–49	4722 (98.1)	94 (2.0)	Ref	
50–56	3045 (96.9)	97 (3.1)	0.62	0.47–0.83
57–63	1228 (95.5)	58 (4.5)	0.42	0.30–0.58
Total patients	13,066 (97.7)	307 (2.3)		
Poverty level (% FPL)				
0–100	9466 (97.8)	213 (2.2)	0.95	0.74–1.23
>100	3600 (97.5)	94 (2.5)	Ref	
Race/ethnicity				
Hispanic/Latino	6074 (97.7)	141 (2.3)	Ref	
White	3163 (97.8)	72 (2.2)	1.02	0.76–1.37
African American	1228 (97.2)	35 (2.8)	0.90	0.62–1.31
Asian	1146 (97.8)	26 (2.2)	1.02	0.67–1.57
Other/declined	1454 (97.8)	33 (2.2)	1.08	0.74–1.59
Patient age (years)				
<18	597 (98.7)	8 (1.3)	1.44	0.70–2.98
18–24	6560 (98.1)	124 (1.9)	Ref	
25–29	3233 (97.5)	84 (2.5)	0.72	0.54–0.96
30–34	1556 (96.5)	57 (3.5)	0.51	0.37–0.70
35–39	829 (97.0)	26 (3.0)	0.58	0.37–0.89
40+	291 (97.3)	8 (2.7)	0.68	0.33–1.40

OR, odds ratio; CI, confidence interval.

Table 3

Hospitalizations for infection or transfusion in women having a medical abortion with mifepristone 200 mg and misoprostol 800 mcg buccally (N= 13,373)

Gestational age	Patients n	Infections n (%)	Transfusions n (%)
22–28 days	554	0 (0.00)	1 (0.18)
29–35 days	1080	1 (0.09)	0 (0.00)
36–42 days	2495	0 (0.00)	0 (0.00)
43–49 days	4816	1 (0.02)	0 (0.00)
50–56 days	3142	0 (0.00)	3 (0.10)
57–63 days	1286	0 (0.00)	0 (0.00)
Total	13,373	2 (0.01)	4 (0.03)



Table 5

Loss to follow-up analysis among women having a medical abortion with mifepristone 200 mg and misoprostol 800 mcg buccally (N=13,373)

	Completed follow-up n (%)	Lost to follow-up n (%)	OR <sup>a</sup>	95% CI
Gestational age (days)				
22–28	554 (85.1)	97 (14.9)	1.00	0.79–1.25
29–35	1080 (86.3)	172 (13.7)	0.91	0.76–1.08
36–42	2495 (85.6)	419 (14.4)	0.96	0.84–1.09
43–49	4816 (85.1)	845 (14.9)	Ref	
50–56	3142 (83.0)	645 (17.0)	1.17	1.05–1.31
57–63	1286 (81.7)	288 (18.3)	1.28	1.10–1.48
Poverty level (% FPL)				
0–100	9679 (83.7)	1887 (16.3)	1.24	1.12–1.38
>100	3694 (86.5)	579 (13.6)		
Race/ethnicity				
Hispanic/Latino	6215 (84.1)	1173 (15.9)		
White	3235 (83.4)	643 (16.6)	1.05	0.95–1.17
African American	1263 (82.8)	262 (17.2)	1.10	0.95–1.27
Asian	1172 (91.1)	115 (8.9)	0.52	0.43–0.64
Other/declined	1487 (84.5)	273 (15.5)	0.97	0.84–1.12
Patient age (years)				
<18	605 (80.0)	152 (20.0)	1.42	1.17–1.71
18–24	6684 (84.9)	1186 (15.1)		
25–29	3317 (83.7)	646 (16.3)	1.10	0.99–1.22
30–34	1613 (84.8)	289 (15.2)	1.01	0.88–1.16
35–39	855 (84.6)	156 (15.4)	1.03	0.86–1.23
40+	299 (89.0)	37 (11.0)	0.70	0.49–0.99

OR, odds ratio; CI, confidence interval.

<sup>a</sup> OR represents odds of being lost to follow-up.

48–72 h later is safe and effective through 63 days estimated gestational age. Further, need for aspiration for any reason was low, the chance of needing aspiration increased with gestational age at the time of medical abortion, and the frequency of hospitalization was rare. This study reinforces the safety and efficacy of the evidence-based regimen for medical abortion, and contributes to the evidence against restrictions that require use of the FDA-approved regimen.

## References

- [1] Peyron R, Aubeny E, Targosz V, Silvestre L, Renault M, Elkik F, et al. Early termination of pregnancy with mifepristone (RU-486) and the orally active prostaglandin misoprostol. *N Engl J Med* 1993;328:1509–13.
- [2] Aubeny E, Peyron R. Termination of early pregnancy (up to and after 63 days of amenorrhea) with mifepristone (RU 486) and increasing doses of misoprostol (vol 40, pg 85, 1995). *Int J Fertil Menopausal Stud* 1996;41:56.
- [3] Spitz I, Bardin C, Benton L, Robbins A. Early pregnancy termination with mifepristone and misoprostol in the United States. *N Engl J Med* 1998;338:1241–7.
- [4] Schaff E, Eisinger S, Stadalius L, Franks P, Gore B, Poppema S. Low-dose mifepristone 200 mg and vaginal misoprostol for abortion. *Contraception* 1999;59:1–6.
- [5] World Health Organization Task Force on Post-Ovulatory Methods of Fertility Regulation. Comparison of two doses of mifepristone in combination with misoprostol for early medical abortion: a randomised trial. *Br J Obstet Gynaecol* 2000;107:524–30.
- [6] Schaff E, Fielding S, Westhoff C, Ellertson C, Eisinger S, Stadalius L, et al. Vaginal misoprostol administered 1, 2, or 3 days after mifepristone for early medical abortion—a randomized trial. *JAMA* 2000;284:1948–53.
- [7] Schaff E, Fielding S, Westhoff C. Randomized trial of oral versus vaginal misoprostol at one day after mifepristone for early medical abortion. *Contraception* 2001;64:81–5.
- [8] Winikoff B, Dzuba IG, Creinin MD, Crowden WA, Goldberg AA, Gonzales J, et al. Two distinct oral routes of misoprostol in mifepristone medical abortion: a randomized controlled trial. *Obstetrics & Gynecology* 2008;112:1303–10.
- [9] Winikoff B, Dzuba IG, Chong E, Goldberg AB, Lichtenberg ES, Ball C, et al. Extending outpatient medical abortion services through 70 days of gestational age. *Obstet Gynecol* 2012;120:1070–6.
- [10] Fjerstad M, Sivin I, Lichtenberg ES, Trussell J, Cleland K, Cullins V. Effectiveness of medical abortion with mifepristone and buccal misoprostol through 59 gestational days. *Contraception* 2009;80:282–6.
- [11] Cleland K, Creinin MD, Nucatola D, Nshom M, Trussell J. Significant adverse events and outcomes after medical abortion. *Obstet Gynecol* 2013;121:166–71.
- [12] Boonstra H. Medication abortion restrictions burden women and providers—and threaten US trend toward very early abortion. *Guttmacher Policy Rev* 2013;16:18–23.
- [13] Steward R, Melamed A, Kim R, Nucatola D, Gatter M. Infection and extramural delivery with use of digoxin as a feticidal agent. *Contraception* 2012;85:150–4.
- [14] Grossman DA, Grindlay K, Buchacker T, Potter JE, Schmettmann CP. Changes in service delivery patterns after introduction of telemedicine provision of medical abortion in Iowa. *Am J Public Health* 2013;103:73–8.
- [15] Clark W, Bracken H, Tanenhaus J, Schweikert S, Lichtenberg ES, Winikoff B. Alternatives to a routine follow-up visit for early medical abortion. *Obstet Gynecol* 2010;115:264–72.
- [16] Horning EL, Chen BA, Meyn LA, Creinin MD. Comparison of medical abortion follow-up with serum human chorionic gonadotropin testing and in-office assessment. *Contraception* 2012;85:402–7.
- [17] Haimov-Kochman R, Arbel R, Sciaky-Tamir Y, Brzezinski A, Laufer N, Yagel S. Risk factors for unsuccessful medical abortion with mifepristone and misoprostol. *Acta Obstet Gynecol Scand* 2007;86:462–6.

# Exhibit 35

2019 Citizen Petition of Am. Ass'n of Pro-Life  
Obstetricians & Gynecologists to FDA (Mar. 29, 2019)

## Citizen Petition

March 29, 2019

The undersigned submit this petition to request the Commissioner of Food and Drugs to: (I) restore and strengthen elements of the Mifeprex regimen and prescriber requirements approved in 2000, and (II) retain the Mifeprex Risk Evaluation and Mitigation Strategy (REMS), and continue limiting the dispensing of Mifeprex to patients in clinics, medical offices, and hospitals, by or under the supervision of a certified prescriber.

### A. Action Requested

#### I. RESTORE AND STRENGTHEN ELEMENTS OF THE MIFEPREX REGIMEN AND PRESCRIBER REQUIREMENTS APPROVED IN 2000.

Current language and requested language for the Mifeprex Label and the Mifeprex *Risk Evaluation and Mitigation Strategy* (REMS) are included in Exhibit A.<sup>1</sup> Requests include:

**A. Indications and Usage.** Mifeprex, in a regimen with misoprostol, for the termination of intrauterine pregnancy, should be limited to 49 days' gestation.

#### B. Dosage and Administration.

1. Mifeprex should be administered by or under the supervision of a physically present and certified physician who has ruled out ectopic pregnancy.
2. The use of Mifeprex and misoprostol for the termination of pregnancy should require three office visits by the patient.

**C. Contraindications.** Mifeprex use is contraindicated for patients who do not have convenient access to emergency medical care.

**D. Adverse Event Reporting.** Certified prescribers, emergency medical personnel, physicians treating complications, and Danco Laboratories should report to FDA's MedWatch Reporting system any deaths, hospitalizations, blood transfusions, emergency room visits, failures requiring surgical completion, ongoing pregnancy, or other major complications following the use of Mifeprex and misoprostol.

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<sup>1</sup> Other documents will require corresponding modifications, including the Mifeprex Medication Guide, Prescriber Agreement Form, and Patient Agreement Form.



**E. Additional studies.** The Mifeprex REMS should require a formal study of outcomes for at-risk populations, including: patients under the age of 18; patients with repeat Mifeprex abortions; patients who have limited access to emergency room services; and patients who self-administer misoprostol.

II. RETAIN THE MIFEPREX RISK EVALUATION AND MITIGATION STRATEGY (REMS), AND CONTINUE LIMITING THE DISPENSING OF MIFEPREX TO PATIENTS IN CLINICS, MEDICAL OFFICES, AND HOSPITALS, BY OR UNDER THE SUPERVISION OF A CERTIFIED PRESCRIBER.

**A. Retain the Mifeprex REMS.**

**B. Continue limiting the dispensing of Mifeprex to patients in clinics, medical offices, and hospitals, by or under the supervision of a certified prescriber.**

1. Mifeprex should be dispensed only in clinics, medical offices, and hospitals.

a. **The “TelAbortion” Direct-to-Consumer Mifeprex Study**

b. **The Mifeprex through Pharmacy Dispensing Study**

c. **Beyond the Current Studies**

2. Mifeprex Prescribers Should be Certified.

## B. Statement of Grounds

### I. RESTORE AND STRENGTHEN ELEMENTS OF THE MIFEPREX REGIMEN AND PRESCRIBER REQUIREMENTS APPROVED IN 2000.<sup>2</sup>

**A. Indications and Usage.** Mifeprex, in a regimen with misoprostol, for the termination of intrauterine pregnancy, should be limited to 49 days' gestation.

In 2016, FDA increased the maximum gestational age for Mifeprex use for abortion from 49 days (7 weeks) to 70 days (10 weeks), and changed the method of administration of misoprostol from oral to buccal (*i.e.*, in the cheek pouch). However drug-induced abortion<sup>3</sup> regimens demonstrate an increase in complications and failures after 49 days' gestation.

In a 2011 study of thousands of patients, the majority of whom had a drug-induced abortion using what is now the Mifeprex regimen, the rate of infection and the rate of failure requiring surgical intervention increased with gestational age.<sup>4</sup> The American College of Obstetricians and Gynecologists (ACOG) has stated: “the risk of clinically significant bleeding and transfusion may be lower in women who undergo medical abortion of gestations up to 49 days compared with those who undergo medical abortion of gestations of more than 49 days.”<sup>5</sup>

Further, a 2015 meta-analysis examined all the existing publications on buccal administration of misoprostol, 20 studies in all, from November 2005 through January 2015. The failure rate of the buccal misoprostol regimen increased as the gestational age

<sup>2</sup> The FDA approved Mifeprex for use in the United States on September 28, 2000, with safeguards considered necessary to ensure patient safety. The drug's initial approval was for termination of pregnancy, in a regimen with misoprostol, through 49 days of pregnancy. FDA significantly modified the drug's label at the application of the manufacturer, Danco Laboratories, in 2016, extending approved use to 70 days of pregnancy. Additional changes included: a new dosage of both Mifeprex and misoprostol; permitting home administration of Mifeprex and misoprostol; a new route of administration for the misoprostol (buccal, in the cheek pouch); permitting non-physicians to become certified prescribers; a decrease from 3 to 1 mandatory office visits by the patient; and reduced reporting requirements. U.S. Gov't Accountability Office, GAO-18-292, Food and Drug Administration: Information on Mifeprex Labeling Changes and Ongoing Monitoring Efforts 4-7 (2018); Mifeprex Risk Evaluation and Mitigation Strategy (REMS), [https://www.accessdata.fda.gov/drugsatfda\\_docs/remis/Mifeprex\\_2016-03-29\\_REMS\\_full.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/remis/Mifeprex_2016-03-29_REMS_full.pdf); Mifeprex Medication Guide, <https://www.fda.gov/downloads/Drugs/DrugSafety/ucm088643.pdf>.

<sup>3</sup> The terms “Medication abortion,” “medical abortion,” “chemical abortion,” and “drug-induced abortion” [or termination of pregnancy] share the same meaning and refer to the use of abortion-inducing drugs, rather than surgery, to induce abortion. The current FDA-approved regimen uses two drugs, mifepristone (a.k.a. Mifeprex or RU-486) and misoprostol.

<sup>4</sup> Mentula MJ, Niinimäki M, Suhonen S, Hemminki E, Gissler M, and Heikinheimo O, *Immediate Adverse Events after Second Trimester Medical Termination of Pregnancy: Results of a Nationwide Registry Study*, Human Reproduction 26(4), 927-932 (2011).

<sup>5</sup> ACOG Practice Bulletin 143: *Medical Management of First-Trimester Abortion*, p. 5 (Mar. 2014, reaffirmed 2016).

increased, especially at gestational ages greater than 49 days.<sup>6</sup> The current FDA label also acknowledges this fact.<sup>7</sup>

Given the serious risks of failure, hemorrhage, infection, and ongoing pregnancy that increase as pregnancy advances, the gestational limit for the Mifeprex regimen should have never been increased.

## **B. Dosage and Administration.**

1. Mifeprex should be administered by or under the supervision of a physically present and certified physician who has ruled out ectopic pregnancy.

The 2000 Mifeprex regimen required Mifeprex to be “provided by or under the supervision of a *physician*” who meets qualifications discussed in this section below.<sup>8</sup> However, the 2016 regimen replaced “physician” with “healthcare provider,” thus permitting non-physicians to apply to be certified prescribers.<sup>9</sup> Given the regimen’s serious risks, the FDA should limit the ability to prescribe and dispense Mifeprex to qualified, licensed physicians. Physicians are better trained to diagnose patients who have contraindications to Mifeprex and to verify gestational age.

The current Mifeprex Risk Evaluation and Mitigation Strategy (REMS), discussed in Section II below, continues to provide that “Mifeprex must be dispensed to patients only in certain healthcare settings, specifically clinics, medical offices, and hospitals, *by or under the supervision of a certified prescriber.*”<sup>10</sup> Yet, abortion providers today are promoting and performing “telemedicine abortions,” where the certified prescriber’s “supervision” of the dispensing of Mifeprex is limited to a videoconference.<sup>11</sup> This practice demonstrates a flagrant disregard for FDA safeguards.

To ensure true supervision, the FDA should require certified prescribers to be physically present when Mifeprex is dispensed so that they can appropriately examine patients and rule out contraindications to the use of Mifeprex. This requirement would be consistent with other requirements in the Mifeprex Label and REMS.

<sup>6</sup> Chen MJ, Creinin MD, *Mifepristone with Buccal Misoprostol for Medical Abortion*, Obstet. Gynecol 126 (1) July 2015 12-21.

<sup>7</sup> Mifeprex 2016 label, [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2016/020687s020lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020687s020lbl.pdf).

<sup>8</sup> Mifeprex 2000 label, Dosage and Administration, emphasis added.

<sup>9</sup> Mifeprex 2016 label, [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2016/020687s020lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020687s020lbl.pdf).

<sup>10</sup> Mifeprex 2016 REMS, emphasis added,

[https://www.accessdata.fda.gov/drugsatfda\\_docs/remis/Mifeprex\\_2016-03-29\\_REMS\\_full.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/remis/Mifeprex_2016-03-29_REMS_full.pdf).

<sup>11</sup> See Planned Parenthood Releases New Educational Video on Telemedicine Abortion (Feb. 6, 2018), <https://www.plannedparenthood.org/about-us/newsroom/press-releases/planned-parenthood-releases-new-educational-video-on-telemedicine-abortion>.

In the Mifeprex Label, the FDA emphasizes that “Mifeprex is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS)” because of the drug’s “risks of serious complications.” In a bold-print box, the FDA states that before prescribing Mifeprex, a provider must inform a patient: about the risks of serious events; whom to call and what to do if certain symptoms occur; and to take the Medication Guide with her if she visits an emergency room or healthcare provider who did not prescribe Mifeprex, so that she receives appropriate, informed care.<sup>12</sup>

Further, a provider must sign a Provider Agreement Form, attesting that he or she can:

- **Assess the duration of pregnancy accurately.**<sup>13</sup> Failures and complications of Mifeprex abortion increase with increasing gestational age. Mifeprex use is approved through 70 days’ gestation.<sup>14</sup> FDA should strengthen this requirement by mandating that gestational age be accurately assessed by ultrasound in order to both ensure compliance with FDA restrictions and adequately inform the patient of gestational age-specific risks, which rise with increasing gestational age.
- **Diagnose ectopic pregnancies**<sup>15</sup> (*i.e.*, extrauterine pregnancy; pregnancy outside the uterus), which Mifeprex cannot end. When an ectopic pregnancy progresses, it can rupture the fallopian tube, causing bleeding, severe pain, or death. If a woman with an extrauterine pregnancy is given Mifeprex, she may believe the symptoms for ectopic pregnancy are simply the side effects of drug-induced abortion, which are similar. As of December 31, 2017, at least 97 women with ectopic pregnancies in the United States had been given Mifeprex.<sup>16</sup> Of these women, at least two bled to death from an undiagnosed ectopic pregnancy.<sup>17</sup> They likely did not recognize that their cramps, abdominal pain, and perhaps vaginal bleeding were dangerous—not side effects expected in a Mifeprex abortion.<sup>18</sup>

<sup>12</sup> Mifeprex 2016 label, [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2016/020687s0201bl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020687s0201bl.pdf).

<sup>13</sup> Mifeprex Prescriber Agreement Form, [https://www.accessdata.fda.gov/drugsatfda\\_docs/remis/Mifeprex\\_2016-03-29\\_Prescriber\\_Agreement\\_Form.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/remis/Mifeprex_2016-03-29_Prescriber_Agreement_Form.pdf).

<sup>14</sup> See Section I.A, *supra*.

<sup>15</sup> Mifeprex Prescriber Agreement Form, [https://www.accessdata.fda.gov/drugsatfda\\_docs/remis/Mifeprex\\_2016-03-29\\_Prescriber\\_Agreement\\_Form.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/remis/Mifeprex_2016-03-29_Prescriber_Agreement_Form.pdf).

<sup>16</sup> Mifepristone U.S. Post-Marketing Adverse Events Summary through 12/31/2017, RCM # 2007-525, NDA 20-687, <https://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM603000.pdf>.

<sup>17</sup> *Id.*

<sup>18</sup> Donna Harrison, M.D. & Michael J. Norton Testimony before the Iowa Board of Medicine, p. 3 (Aug. 21, 2013), *citing* Postmarket Drug Safety Information for Patients and Providers, Questions and Answers on Mifeprex,

- **Provide surgical intervention if needed, or has made plans to provide such care through others.**<sup>19</sup> He or she must assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.<sup>20</sup>

Clearly, a provider who does not physically meet with and examine a patient, but simply consults with the patient over the Internet, is not capable of fulfilling these requirements, or of ruling out additional contraindications (*i.e.*, circumstances that make a treatment or medication *unadvisable*) to Mifeprex use. These physical contraindications include pelvic infections, ovarian masses, cardiac arrhythmias, and liver abnormalities.<sup>21</sup> A physician bears responsibility to diagnose and rule out contraindications prior to Mifeprex use. It is inadequate to entrust this critical care to another healthcare provider who is not trained in diagnosis. Further, a healthcare provider who is not physically accessible to a patient cannot provide adequate follow-up care to patients, as required by the FDA Mifeprex regimen.

Thirty-four states permit only physicians to prescribe Mifeprex,<sup>22</sup> with nineteen states requiring the provider to be physically present with the patient.<sup>23</sup> For example, the law in Alabama states that the physical presence and care of a physician are necessary because “the failure and complications from medical abortion increase with advancing gestational age, because the physical symptoms of medical abortion can be identical to the symptoms of ectopic pregnancy, and because abortion-inducing drugs do not treat ectopic pregnancies but rather are contraindicated in ectopic pregnancies.”<sup>24</sup>

Lawmakers in these states recognize that abortion providers cannot diagnose contraindications and cannot adequately care for their patients through a videoconference. Fundamentally, telemedicine “may be legitimate when it comes to discrete, document-based tasks such as reading X-rays,” but it “is not the standard of care when it comes to abortion or the management of miscarriage.”<sup>25</sup>

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<https://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm492705.htm>.

<sup>19</sup> Mifeprex Prescriber Agreement Form,

[https://www.accessdata.fda.gov/drugsatfda\\_docs/remis/Mifeprex\\_2016-03-29\\_Prescriber\\_Agreement\\_Form.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/remis/Mifeprex_2016-03-29_Prescriber_Agreement_Form.pdf).

<sup>20</sup> *Id.*

<sup>21</sup> Harrison & Norton Testimony, p. 3.

<sup>22</sup> Donovan MK, *Self-Managed Medication Abortion: Expanding the Available Options for U.S. Abortion Care*, Guttmacher Policy Review, Vol. 21, p. 44 (2018).

<sup>23</sup> *Id.*

<sup>24</sup> Ala. Code § 26-23E-7.

<sup>25</sup> Harrison & Morton Testimony, p. 19.

2. The use of Mifeprex and misoprostol for the termination of pregnancy should require three office visits by the patient.

The 2016 regimen significantly diminished doctor-patient interaction. While the 2000 Mifeprex label required three patient visits with the abortion provider, women may now obtain Mifeprex at a clinic and self-administer it at home. They are no longer required to return to the clinic for the administration of misoprostol, which prevents abortion providers from ensuring that they take the drugs at the correct times. Further, providers may now “confirm” that a patient’s drug-induced abortion was successful without a clinic visit,<sup>26</sup> increasing the threat that Rh-negative patients will not receive administration of Rhogam, which is necessary to prevent serious risks in subsequent pregnancies.

The 2016 regimen directs that patients be given or prescribed misoprostol to take 24 to 48 hours after taking Mifeprex. However, without monitoring, a patient may take misoprostol before 24 hours have passed since she consumed Mifeprex, rendering the regimen ineffective and increasing the likelihood that she will experience a failed drug-induced abortion and require surgery.

Using buccal misoprostol sooner than 24 hours after administering mifepristone leads to a significantly increased failure rate. In one study investigating the timing of buccal misoprostol after mifepristone, nearly one out of every three to four women who took buccal misoprostol shortly after mifepristone failed to abort.<sup>27</sup> The failure rate ranged from 27% to 31%, depending on the pregnancy gestation.<sup>28</sup> Given these results, the authors of this study strongly recommended that buccal misoprostol not be taken immediately after mifepristone because of the very high abortion failure rate.<sup>29</sup> However, with home administration of misoprostol, healthcare providers have no control over when their patients consume the drug.

A woman may also choose to swallow misoprostol rather than keep the pill between her cheek and gum for 30 minutes, converting a “buccal” administration into an “oral” administration. An oral administration of misoprostol following the lower dose of mifepristone in the current regimen is not as effective in ending the pregnancy.

Further, waiting until 24 hours after Mifeprex to administer misoprostol does not guarantee success, and the failure rate of buccal misoprostol is higher than that under the 2000 regimen. A comprehensive systematic review and meta-analysis of the existing

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<sup>26</sup> See Mifeprex 2016 label,

[https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2016/020687s0201bl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020687s0201bl.pdf).

<sup>27</sup> Lohr PA, Reeves MF, Hayes JL, Harwood B, Creinin MD, *Oral Mifepristone and buccal misoprostol administered simultaneously for abortion: a pilot study*, *Contraception* 76 (2007) 215-220.

<sup>28</sup> *Id.*

<sup>29</sup> *Id.*



studies of the 2016 regimen found that women who take misoprostol earlier than 48 hours after mifepristone are more likely to fail the regimen.<sup>30</sup>

Under the 2000 regimen, doctors were also able to provide care to patients during the most challenging and painful time in the drug-induced abortion. According to the World Health Organization, up to 90% of women will abort within 4-6 hours after taking misoprostol.<sup>31</sup> The 2000 regimen permitted a patient to be in a clinic for this period of time, during which she would be under the observation and care of medical personnel. This observation period is for “both patient safety and compassion. . . . This is the time when women should be in a place where their bleeding can be monitored, their vital signs can be observed by trained medical personnel, and they can receive sufficient pain medication during the most difficult part of the expulsion.”<sup>32</sup>

Abortion complications are also more frequent when women abort at home, without the oversight of a healthcare provider. A 2018 combined retrospective and longitudinal follow-up study of complications related to induced abortion in Sweden determined that “[t]he complication frequency [of drug-induced abortion] was significantly higher among women <7 gestational weeks who had their abortions *at home*.”<sup>33</sup>

In-person contact with a healthcare provider is critical to post-abortion care as well. Abortion providers should perform a “follow-up [physical exam] after the use of mifepristone in order to confirm abortion and rule out life-threatening infection.”<sup>34</sup> Before FDA approved the 2016 regimen, the follow-up visit was considered “very important to confirm by clinical examination or ultrasonographic scan that a complete termination of pregnancy has occurred.”<sup>35</sup> In fact, the 2000 label provided that “[e]ach patient must understand the necessity of completing the treatment schedule, including a follow-up visit approximately 14 days after taking Mifeprex.”<sup>36</sup> ACOG’s current policy explains that:

Women are not good candidates for medical abortion if they ... desire quick completion of the abortion process [or] are not available for follow-up contact or evaluation....<sup>37</sup>

<sup>30</sup> Chen MJ, Creinin MD, *Mifepristone with Buccal Misoprostol for Medical Abortion*, Obstet.Gynecol 126 (1) July 2015 12-21.

<sup>31</sup> World Health Organization, *Safe Abortion: Technical and Policy Guidance for Health Systems* 45.

<sup>32</sup> Donna Harrison, M.D., Aff. *Okla. Coalition for Reproductive Justice v. Cline*, Case No. CV-2014-1886 (Feb. 24, 2015) ¶ 136.

<sup>33</sup> Carlsson I, Breiding K, and Larsson PG, *Complications Related to Induced Abortion: a Combined Retrospective and Longitudinal Follow-up Study*, BMC Women’s Health (2018) 18:158, p. 4 (emphasis added).

<sup>34</sup> Harrison & Norton Testimony, p. 18.

<sup>35</sup> Mifeprex 2000 label, Day 14: Post-Treatment Examination.

<sup>36</sup> Mifeprex 2000 label, Information for Patients.

<sup>37</sup> ACOG Practice Bulletin 143, p. 6.

In addition to ensuring for all drug-induced abortion patients that the uterus has been emptied of retained tissue and that they are not suffering from infection, the follow-up examination is particularly critical for Rh-negative patients. These patients must be administered Rhogam in order to prevent Rh isoimmunization in subsequent pregnancies. Without follow-up, women will not receive the Rhogam after the abortion, greatly increasing their risk of subsequent Rh isoimmunization, which can endanger future pregnancies.<sup>38</sup>

Nonetheless, abortion advocates strongly supported the reduction in required visits, and continue to advocate for the elimination of direct provider-patient contact. Gynuity Health Projects (an organization that “has been at the forefront of efforts to increase women’s access to medical abortion in settings throughout the world”)<sup>39</sup> has conducted at least three domestic and five international studies<sup>40</sup> on eliminating pelvic ultrasound or exam after drug-induced abortion. Following one study, researchers determined that “[s]emi-quantitative pregnancy tests ... could be used in lieu of transvaginal ultrasound and/or serum hCG at clinic-based follow-up or by women themselves for home-based follow-up.”<sup>41</sup>

In a more recent study, researchers asserted that the “common practice of scheduling a clinical contact after every medical abortion may not be necessary to ensure safety; enabling patients to determine for themselves whether or not a contact is needed can be a

<sup>38</sup> ACOG Practice Bulletin 181: *Prevention of Rh D Alloimmunization* (Aug. 2017); and SOGC Clinical Practice Guidelines: *Prevention of Rh Alloimmunization* (No. 133, Sept. 2003).

<sup>39</sup> See Gynuity Health Projects, Medical Abortion, <https://gynuity.org/programs/medical-abortion>. Founded by Beverly Winikoff, M.D., M.P.H., in 2003, Gynuity outlines on its “Medical Abortion” page the organization’s research projects, including efforts to: “Develop innovative service delivery systems through telemedicine; Simplify and de-medicalize medical abortion services; Expand access to medical abortion in the 1<sup>st</sup> and 2<sup>nd</sup> trimesters of pregnancy; Conduct clinical research to develop new abortion medications; Develop a ‘missed menses pill’/menstrual regulation method; Develop additional clinical indications for mifepristone.” Gynuity has launched a “coalition to expand access to mifepristone in the United States,” co-created a “medical abortion commodities database,” “introduce[d] medical abortion in new settings,” “incorporate[ed] new clinical evidence into service guidelines,” and “expanded medical abortion access through education and local champions.”

<sup>40</sup> See, e.g., *Self-Assessment of Medical Abortion Outcome Using Serial Multi-level Pregnancy Tests* [NCT02570204] (Sept. 2015 – Dec. 2016), <https://www.clinicaltrials.gov/ct2/show/NCT02570204?term=Self-Assessment+of+Medical+Abortion+Outcome+Using+Serial+Multi-level+Pregnancy&rank=1>; *Exploring the Role of At-home Semi-Quantitative Pregnancy Tests for Medical Abortion Follow-up* [NCT01150279] (Aug. 2009 – May 2014), <https://www.clinicaltrials.gov/ct2/show/NCT01150279?term=Exploring+the+Role+of+At-home+Semi-Quantitative+Pregnancy+Tests+for+Medical+Abortion+Follow-up&rank=1>; *De-Medicalizing Mifepristone Medical Abortion* [NCT00120224] (May 2005 – Apr. 2007), <https://www.clinicaltrials.gov/ct2/show/NCT00120224?term=De-Medicalizing+Mifepristone+Medical+Abortion&rank=1>.

<sup>41</sup> Lynd K, et al., *Simplified Medical Abortion Using a Semi-Quantitative Pregnancy Test for Home-Based Follow-up*, *Int J Gynaecol Obstet.* 2013 May;121(2):144-8.

reasonable approach.”<sup>42</sup> They reached this conclusion even with 26% of participants failing to provide sufficient follow-up information.<sup>43</sup>

Gynuity researchers also conducted a recent systematic review of existing studies on “the accuracy and acceptability of a strategy for identifying ongoing pregnancy after medical abortion treatment using a low-sensitivity pregnancy test (LSPT).” While the researchers acknowledged that “the LSPT strategy had *moderate* sensitivity for identifying ongoing pregnancy” and “the LSPT itself had a limited role in the detection of treatment failures [*i.e.*, ongoing pregnancy] in the studies,” they stated that the “LSPT strategy shows promise for reducing the need for in-person follow-up after medical abortion. A range of home-based options should be validated to meet the varied needs of women and abortion providers in diverse settings.”<sup>44</sup>

In reality, a de-emphasis on follow-up care increases risks of post-abortion complications. As discussed above, the 2000 regimen’s requirement that women return approximately 14 days after ingesting mifepristone was considered necessary to ensure that all pregnancy tissue had been passed.<sup>45</sup> This determination is crucial, because retained pregnancy tissue can lead to continued bleeding and serious intrauterine infections. The return visit permits healthcare providers to ensure that a patient is not experiencing these or other complications from the abortion procedure, and that Rh negative patients are administered Rhogam to protect future pregnancies.

Abortion advocates argue that three clinic visits make accessing abortion-inducing drugs more difficult for patients with transportation challenges; however, as noted above, ACOG acknowledges that drug-induced abortion is *contraindicated* for patients who “are not available for follow-up contact or evaluation.”<sup>46</sup> Surgical abortion is a better choice for these patients, because it “[d]oes not require follow-up in most cases.”<sup>47</sup>

Drug-induced abortion is a longer process that requires more attention and care from healthcare providers. Three visits to a physician in the interest of patient safety should not be sacrificed for the convenience of healthcare providers or even their patients.

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<sup>42</sup> Raymond EG, et al., *Self-assessment of Medical Abortion Outcome Using Symptoms and Home Pregnancy Tests*, *Contraception* 97 (2018) 324-28.

<sup>43</sup> *Id.*

<sup>44</sup> Raymond EG, et al., *Low-sensitivity Urine Pregnancy Testing to Assess Medical Abortion Outcome: A Systematic Review*, *Contraception* (2018), <https://doi.org/10.1016/j.contraception.2018.03.013> (emphasis added).

<sup>45</sup> Mifeprex 2000 label, Day 14: Post-Treatment Examination.

<sup>46</sup> ACOG Practice Bulletin 143, p. 6.

<sup>47</sup> *Id.*

**C. Contraindications.** Mifeprex use is contraindicated for patients who do not have convenient access to emergency medical care.

The 2000 Mifeprex Label stated:

Because it is important to have access to appropriate medical care if an emergency develops, the treatment procedure is contraindicated if a patient does not have adequate access to medical facilities equipped to provide emergency treatment of incomplete abortion, blood transfusions, and emergency resuscitation during the period from the first visit until discharged by the administering physician.<sup>48</sup>

This critical language was excluded from the 2016 Mifeprex Label. Yet, studies comparing the outcome of surgical versus drug-induced abortion “have clearly demonstrated that Mifeprex abortions have a greater risk of hemorrhage, infection, continued pregnancies, retained tissue and need for emergency reoperation than surgical abortions.”<sup>49</sup> ACOG acknowledges that “[c]ompared with surgical abortion, medical abortion takes longer to complete, requires more active patient participation, and is associated with higher reported rates of bleeding and cramping,” and has lower success rates.<sup>50</sup>

Drug-induced abortion is optional. If a woman does not meet the criteria necessary to use abortion-inducing drugs, then surgical abortion is still an option. For women with transportation difficulties, an abortion provider can complete surgical abortion “in a predictable period of time,” and the procedure “[d]oes not require follow-up in most cases.”<sup>51</sup>

Efforts to promote abortion-inducing drugs to women in rural areas where access to emergency medical care is scarce are detrimental to women’s health. It is better for a patient in a remote region to have a surgical abortion, “which requires a single visit, and is less likely to result in serious or life-threatening complications.”<sup>52</sup>

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<sup>48</sup> Mifeprex 2000 label, Contraindications.

<sup>49</sup> Harrison Aff. ¶ 115.

<sup>50</sup> ACOG Practice Bulletin 143, p. 3 & Box 1.

<sup>51</sup> *Id.*

<sup>52</sup> Harrison & Norton p. 9.

**D. Adverse Event Reporting.** Certified prescribers, emergency medical personnel, physicians treating complications, and Danco Laboratories should report to FDA’s MedWatch Reporting system any deaths, hospitalizations, blood transfusions, emergency room visits, failures requiring surgical completion, ongoing pregnancy, or other major complications following the use of Mifeprex and misoprostol.

The 2016 regimen dramatically reduced accountability for Mifeprex providers by limiting adverse event reporting (AER) requirements, a critical safety mechanism.<sup>53</sup> While prescribers were required to report any serious adverse event associated with Mifeprex under the 2000 label, they are now required to report only deaths associated with Mifeprex.

Even with the 2000 regimen requirements, collecting accurate and complete adverse event information was highly difficult. Adverse events were often not reported or were interpreted by emergency health care providers as the results of spontaneous abortion.<sup>54</sup> The Mifeprex label instructs prescribers to “[a]dvice the patient to take the Medication Guide with her if she visits an emergency room or a healthcare provider who did not prescribe Mifeprex, so that the provider knows that she is undergoing a medical abortion.”<sup>55</sup> Yet, many Mifeprex prescribers violate FDA protocol, instructing their patients to lie to emergency medical personnel. The organization Aid Access instructs patients that if they need to go to an emergency room:

You do not have to tell the medical staff that you tried to induce an abortion; you can tell them that you had a spontaneous miscarriage. Doctors have the obligation to help in all cases and know how to handle a miscarriage. The symptoms of a miscarriage and an abortion with pills are exactly the same and the doctor will not be able to see or test for any evidence of an abortion, as long as the pills have completely dissolved.<sup>56</sup>

Such deception prevents emergency healthcare providers from appropriately caring for their patients, and further decreases the likelihood that adverse events will be reported.

With reduced AER reporting requirements under the 2016 label, what was previously difficult is now virtually impossible. The FDA cannot adequately assess the safety of the current Mifeprex regimen without comprehensive information on adverse events. AERs are the only objective means by which FDA has any data whatsoever on the effects of the

<sup>53</sup> Mifeprex 2016 label.

<sup>54</sup> See GAO-18-292, pp 24-25.

<sup>55</sup> Mifeprex 2016 label, [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2016/020687s020lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020687s020lbl.pdf).

<sup>56</sup> Aid Access, *How do you know if you have complications, and what should you do?*, <https://aidaccess.org/en/page/459/how-do-you-know-if-you-have-complications-and-what-should-you-do>.



Mifeprex regimen on women, and the voluntary and minimal nature of the current AERs means that FDA has no accurate information about the actual number of women injured by drug-induced abortion, or the nature of complications caused by this drug.

After prescribing Mifeprex and misoprostol, certified prescribers should at minimum be required to report the following directly to the FDA Medwatch reporting system, copying Danco Laboratories: deaths, hospitalizations, blood transfusions, emergency room visits, failures requiring surgical completion, ongoing pregnancy, or other major complications. Detailed information must also be included, such as pulse, blood pressure, temperature, pre- and post-transfusion hemoglobin/hematocrit, white blood count, number of units of blood transfused, surgeries, and any other pertinent laboratory or hospital course information, as well as emergency room and hospital discharge diagnoses.

Further, FDA should provide guidance to emergency healthcare providers and physicians responsible for treating complications so that they know how to distinguish complications following drug-induced abortion from complications following spontaneous miscarriage. The guidance should also instruct these providers on how to report adverse events.<sup>57</sup>

The abysmal quality of the current AERs received from Danco Laboratories shows the lack of concern that Danco has demonstrated for the safety of the women who have undergone drug-induced abortion. Responsible reporting is a fundamental safety mechanism that should not be sacrificed in the interest of convenience for abortion providers.

**E. Additional Studies.** The Mifeprex REMS should require a formal study of outcomes for at-risk populations, including: patients under the age of 18; patients with repeat Mifeprex abortions; patients who have limited access to emergency room services; and patients who self-administer misoprostol.

Mifeprex was approved for use in the pediatric population in 2000 after the FDA waived, without explanation, the requirement for studies in the pediatric population. The developmental stage of puberty involves a complex interplay of both progesterone and estrogen effects on the developing female reproductive system. The use, and especially the potential multiple use, of Mifeprex, which is a powerful progesterone blocker, is

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<sup>57</sup> The Self-Induced Abortion Legal Team has created a document titled “Self-Induced Abortion and the Law: What Emergency Room Staff Need to Know.” This document heavily emphasizes patient privacy requirements, including the penalties that healthcare providers may face if they disclose patient information. While these concerns are valid, emergency healthcare providers should also have training on public health reporting requirements and how such reporting does not violate HIPAA or other laws regarding patient privacy. *See*, <https://www.sialegalteam.org>.

likely to significantly impact the developing reproductive system of the adolescent female.<sup>58</sup> It is irresponsible to allow the continued uninvestigated use of Mifeprex in the pediatric female population<sup>59</sup> without requiring long-term studies on the impact of Mifeprex use on pubertal development.

More than one out of every three abortions in the U.S. is a repeat abortion.<sup>60</sup> The repeat use of Mifeprex has been associated in some studies with adverse reproductive health outcomes in future wanted pregnancies.<sup>61</sup> This concern requires further study.

The adverse events of hemorrhage, retained tissue, and infection are common after Mifeprex use. The hemorrhage is often significant enough to warrant transfusion. When patients lack access to emergency medical facilities, such complications could easily translate to deaths. Thus a study of deaths and of severe hemorrhages requiring transfusion should be done to compare outcomes in women with and without access to emergency medical facilities.

## II. RETAIN THE MIFEPREX RISK EVALUATION AND MITIGATION STRATEGY (REMS), AND CONTINUE LIMITING THE DISPENSING OF MIFEPREX TO PATIENTS IN CLINICS, MEDICAL OFFICES, AND HOSPITALS, BY OR UNDER THE SUPERVISION OF A CERTIFIED PRESCRIBER.

### A. Retain the Mifeprex REMS.

Mifeprex, when used for abortion, is subject to a Food and Drug Administration (FDA) *Risk Evaluation and Mitigation Strategy* (REMS) with *elements to assure safe use* (ETASU). FDA determined that the Mifeprex REMS is necessary to ensure the safety and efficacy of the drug, because it carries risks of life-threatening hemorrhage, infection, continued pregnancy, retained tissue, need for emergency surgery, and death. The approved Mifeprex regimen includes the use of another potent drug, misoprostol, which carries its own risks.

Under the Mifeprex REMS with ETASU, a healthcare provider must be certified to prescribe Mifeprex by reviewing the prescribing information and completing a

<sup>58</sup> Arain M, et al., *Maturation of the adolescent brain*, Neuropsychiatric Disease and Treatment, 2013:9 449-461.

<sup>59</sup> Because of their immaturity, minors are also less likely to understand the importance of following prescriber instruction or of recognizing when they need to seek emergency medical treatment.

<sup>60</sup> Jones R, et al., *Which Abortion Patients Have Had a Prior Abortion? Findings from the 2014 U.S. Abortion Patient Survey*, Journal of Women's Health, DOI: 10.1089/jwh.2017.6410 (2014).

<sup>61</sup> Fang L, et al., *Repeated Abortion Affects Subsequent Pregnancy Outcomes in BALB/c Mice*, PLoS ONE 7(10): e48384. doi:10.1371/journal.pone.0048384 (2012).

“Prescriber Agreement Form,” attesting that they can: assess the duration of pregnancy accurately; diagnose ectopic pregnancies; and provide surgical intervention in cases of incomplete abortion or severe bleeding, or designate someone else to provide that care. Further, they must agree to follow the guidelines for use of Mifeprex.

The REMS also requires Mifeprex to “be dispensed to patients only in certain healthcare settings, specifically clinics, medical offices, and hospitals, by or under the supervision of a certified prescriber.” Mifeprex may not be distributed or dispensed through retail pharmacies. Also, a patient must sign a “Patient Agreement Form” and be fully informed of the risks by a certified prescriber. She must receive the Mifeprex Medication Guide, informing her that she needs a “follow-up assessment” 7 to 14 days after she has taken Mifeprex to ensure that she is well and has terminated her pregnancy.<sup>62</sup>

The REMS remains the lone safeguard to monitor and mitigate the risks of death and adverse events from the Mifeprex regimen. Gynuity Health Projects and researchers from the University of California, San Francisco (UCSF) obtained approval from FDA through Investigational New Drug Applications (INDs) to conduct studies that *do not* comply with the Mifeprex REMS. They intend to use the results of these studies to press for the elimination of the Mifeprex REMS.<sup>63</sup> [See Section II.B, below.]

The Mifeprex Medication Guide acknowledges that serious risks accompany FDA’s approved regimen for drug-induced abortion, which includes the use of Mifeprex and another potent drug, misoprostol. The document improperly downplays the risks, however, stating that “*rarely*, serious and potentially life-threatening bleeding, infections, or other problems can occur following . . . medical abortion.” Specifically, “in about 1 out of 100 women [administered Mifeprex and misoprostol] bleeding can be so heavy that it requires a surgical procedure.”<sup>64</sup>

In fact, the internationally used criteria for reporting complications from drugs demonstrate that complications from drug-induced abortions are common, not rare. The Council for International Organizations of Medical Sciences (CIOMS)<sup>65</sup> defines the word

<sup>62</sup> GAO-18-292, pp 4-7 (2018); Mifeprex Risk Evaluation and Mitigation Strategy (REMS), [https://www.accessdata.fda.gov/drugsatfda\\_docs/remis/Mifeprex\\_2016-03-29\\_REMS\\_full.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/remis/Mifeprex_2016-03-29_REMS_full.pdf); 21 U.S.C. § 355-1; Mifeprex Medication Guide, <https://www.fda.gov/downloads/Drugs/DrugSafety/ucm088643.pdf>.

<sup>63</sup> See Daniel Grossman, MD, Research Protocol: *Alternative Provision of Medication Abortion via Pharmacy Dispensing*, Version #:1.3 (July 17, 2018) p. 14.

<sup>64</sup> Mifeprex Medication Guide, <https://www.fda.gov/downloads/Drugs/DrugSafety/ucm088643.pdf>.

<sup>65</sup> The Council for International Organizations of Medical Sciences (CIOMS) is an international, non-governmental, nonprofit organization established jointly by WHO and UNESCO in 1949. Through its membership, CIOMS is representative of a substantial proportion of the biomedical scientific community. In 2013, the membership of CIOMS included 49 international, national, and associate member organizations, representing many of the biomedical disciplines, national academies of sciences, and medical research councils.

“rare” in adverse event reporting as an event that happens in between “1 out of 1,000” to “1 out of 10,000” uses. “Common” is the uniform term used for events that happen in between “1 out of 10” to “1 out of 100” uses.<sup>66</sup> Given that “about 1 out of 100 women” using Mifeprex/misoprostol require surgery, serious complications are common, not rare.<sup>67</sup>

Also, as discussed in Section I.C above, Mifeprex abortions carry greater risks than surgical abortions.<sup>68</sup> A study of over 42,000 women in Finland who had abortions from 2000 to 2006 found that “overall, medical abortion had roughly four times the rate of adverse events than surgical abortion, and hemorrhaging was experienced by 16 percent of medical abortion patients compared with 2 percent of surgical abortion patients.”<sup>69</sup>

A combined retrospective and longitudinal follow-up study of complications related to induced abortion in Sweden published in 2018 determined that the share of complications related to drug-induced abortions at less than 12 weeks *increased* significantly during 2008-2015 without an evident cause. The increase was from 4.2% in 2008 to 8.2% in 2015, with incomplete abortion as the most common complication related to drug-induced abortions at less than 12 weeks.<sup>70</sup>

Abortion advocates are also attacking the REMS by advocating for mifepristone use in spontaneous miscarriage management. In a small recent study, researchers compared the efficacy and safety of using mifepristone with misoprostol for the management of early miscarriages to using misoprostol alone.<sup>71</sup> Notably, 6-10% of study participants had a gestational age of “4-5 weeks gestation.”<sup>72</sup> It is not clear from the authors how participants of that gestational age could meet the published guidelines for diagnosis of non-viable pregnancy recently published by the Society of Radiologists in Ultrasound multispecialty consensus panel.<sup>73</sup> The panel requires the crown-rump length cutoff to 7 mm for embryos without a heartbeat and the mean sac diameter cutoff to 25 mm for

<sup>66</sup> CIOMS training manual on medicine safety,

[http://www.who.int/medicines/areas/quality\\_safety/safety\\_efficacy/trainingcourses/definitions.pdf](http://www.who.int/medicines/areas/quality_safety/safety_efficacy/trainingcourses/definitions.pdf).

<sup>67</sup> See Mifeprex Medication Guide; CIOMS training manual on medicine safety, *supra*.

<sup>68</sup> See Harrison Aff. ¶ 115; ACOG Practice Bulletin 143, p. 3 & Box 1.

<sup>69</sup> GAO-18-292, p. 25, discussing Niinimäki M, et al., *Immediate Complications after Medical Compared with Surgical Termination of Pregnancy*, *Obstetrics & Gynecology*, vol. 114, no. 4 (October 2009): 795-804.

<sup>70</sup> Carlsson I, Breiding K, and Larsson PG, *Complications Related to Induced Abortion: A Combined Retrospective and Longitudinal Follow-up Study*, *BMC Women's Health* (2018) 18:158.

<sup>71</sup> Schreiber CA, et al, *Mifepristone Pretreatment for the Medical Management of Early Pregnancy Loss*, *N Engl J Med* 2018; 378:2161-70.

<sup>72</sup> *Id.* Table 1.

<sup>73</sup> Doubilet PM, Benson CB, Bourne T, et al., *Diagnostic criteria for nonviable pregnancy early in the first trimester*, *N Engl J Med* 2013; 369:1443-1451.

“empty” sacs, in order to minimize interventions that “interrupt a pregnancy that otherwise would have had a normal outcome.”<sup>74</sup>

The authors admit that the study “was not powered to show differences between groups in the proportions of serious adverse events,”<sup>75</sup> an important consideration prior to recommending a change in spontaneous abortion management protocols. Yet, the authors incorrectly stated “such events were rare.”<sup>76</sup> Table 3 gives a total number of serious adverse events as 3.4% for the mifepristone pretreatment group, and 2.0% for the misoprostol alone group.<sup>77</sup> Under the CIOMS criteria for reporting complications from drugs, discussed above, the rate of 2%-3.4% of adverse events in each study arm demonstrates clearly that adverse events are common, not rare, in both misoprostol alone and mifepristone + misoprostol miscarriage management.

Further, the Mifeprex + misoprostol arm raises a concern about the need for further study of adverse events, especially hemorrhage. Mifepristone is known to inhibit endometrial hemostasis (*i.e.*, arrest of bleeding),<sup>78</sup> as demonstrated by many reports of hemorrhage with transfusions reported to the FDA after use of mifepristone and misoprostol for elective abortions.<sup>79</sup>

Of additional concern is the vaginal route of administration of misoprostol. After reports of overwhelming sepsis following vaginal administration of misoprostol, Planned Parenthood changed the route of administration of misoprostol from vaginal to buccal,<sup>80</sup> with subsequent decrease in reported infections. Animal studies have demonstrated that both mifepristone<sup>81</sup> and misoprostol<sup>82</sup> can profoundly suppress innate immunity and the ability to fight infections.

<sup>74</sup> Hu M, Poder L, Filly R, *Impact of New Society of Radiologists in Ultrasound Early First-Trimester Diagnostic Criteria for Nonviable Pregnancy*, J Ultrasound Med 2014; 33:1585–1588.

<sup>75</sup> Schreiber, *supra* p. 2168.

<sup>76</sup> *Id.*

<sup>77</sup> *Id.* p. 2169.

<sup>78</sup> Miech RP, *Pathopharmacology of excessive hemorrhage in mifepristone abortions*, Ann Pharmacother 2007 Dec; 41(12):2002-7.

<sup>79</sup> Gary MM, Harrison DJ. “Analysis of severe adverse events related to the use of mifepristone as an abortifacient.” Ann Pharmacother. 2006 Feb;40(2):191-7; Food and Drug Administration “Mifepristone U.S. Postmarketing Adverse Events Summary” 2011, [https://www.minnpost.com/sites/default/files/attachments/Mifeprex\\_April2011\\_AEs.pdf](https://www.minnpost.com/sites/default/files/attachments/Mifeprex_April2011_AEs.pdf).

<sup>80</sup> Fjerstad M, Trussell J, Sivin I, Lichtenberg ES, Cullins V, *Rates of Serious Infection after Changes in Regimens for Medical Abortion*, N Engl J Med 2009; 361:145-51.

<sup>81</sup> Sternberg EM, Hill JM, Chrousos GP, Kamilaris T, Listwak SJ, Gold PW, Wilder RL, *Inflammatory mediator-induced hypothalamic-pituitary-adrenal axis activation is defective in streptococcal cell wall arthritis-susceptible Lewis rats*, Proc Natl Acad Sci U S A. 1989 Apr;86(7):2374-8; Miech RP, *Pathophysiology of mifepristone-induced septic shock due to Clostridium sordellii*, Ann Pharmacother. 2005 Sep;39(9):1483-8. Epub 2005 Jul 26.

<sup>82</sup> Aronoff DM et al., *Misoprostol impairs female reproductive tract innate immunity against clostridium sordellii*, 180 J. Immunol. 8222-8230 (2008).



Despite the clear methodological errors, including a failure to accurately diagnose fetal death according to accepted criteria as well as lack of adherence to the stated inclusion criteria, and despite the absence of power to evaluate safety, abortion advocates are calling for the routine use of mifepristone to manage spontaneous miscarriages.<sup>83</sup> Any change in spontaneous miscarriage management with mifepristone should require an FDA New Drug Application (NDA) with two randomized controlled trials (RCTs) comparing the arms of mifepristone and misoprostol, misoprostol alone, surgical management, and expectant management. Without blinded RCTs to evaluate not only efficacy but also safety, it is premature to remove the REMS for Mifeprex to facilitate mifepristone access for spontaneous miscarriage management.

Despite the presence of serious risks and contraindications to the Mifeprex regimen, Gynuity, the University of California, San Francisco (UCSF), and other abortion advocates want the FDA to eliminate the remaining safeguards that were enacted to ensure the safety and efficacy of Mifeprex. They are pursuing their goals through publication, advocacy, litigation,<sup>84</sup> and/or controversial research enabled by FDA.<sup>85</sup>

Further, as Section II.B below explains, lifting the REMS is only the starting point for abortion advocates.

**B. Continue limiting the dispensing of Mifeprex to patients in clinics, medical offices, and hospitals, by or under the supervision of a certified prescriber.**

**1. Mifeprex should be dispensed only in clinics, medical offices, and hospitals.**

The Mifeprex REMS requires that Mifeprex “be dispensed to patients only in clinics, medical offices and hospitals, by or under the supervision of a certified prescriber.” That prescriber must be capable of assessing the duration of a pregnancy accurately, diagnosing ectopic pregnancies, and providing or referring for surgical intervention in cases of incomplete abortion or hemorrhaging.<sup>86</sup>

Abortion advocates, however, want the FDA to permit healthcare providers to prescribe Mifeprex to pregnant patients over the Internet or phone, with the drug available at pharmacies or through the mail, and through advance provision (*i.e.*, before a patient is pregnant). Eliminating or relaxing the REMS to facilitate Internet or telephone prescriptions would be dangerous to women and adolescent girls. Healthcare providers

<sup>83</sup> Molly Walker, *Mifepristone: Better for Managing Early Miscarriage*, Medpage Today, (June 6, 2018), <https://www.medpagetoday.com/obgyn/pregnancy/73336>.

<sup>84</sup> *Chelius v. Azar*, CIV. NO. 1:17-cv-00493-DKW-KSC (Dist. Ct. HI 2018).

<sup>85</sup> See Section II.B, below.

<sup>86</sup> Mifeprex Risk Evaluation and Mitigation Strategy (REMS), [https://www.accessdata.fda.gov/drugsatfda\\_docs/rem/s/Mifeprex\\_2016-03-29\\_REMS\\_full.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/rem/s/Mifeprex_2016-03-29_REMS_full.pdf).

prescribing abortion-inducing drugs over the Internet or phone or before a patient is even pregnant cannot adequately evaluate patients for contraindications to the drugs.<sup>87</sup> Further, as discussed above, Rh-negative patients must be administered Rhogam in order to prevent Rh isoimmunization in subsequent pregnancies. Without direct patient contact, women will not receive the Rhogam after the abortion, greatly increasing their risk of subsequent Rh isoimmunization, which can endanger future pregnancies.<sup>88</sup> [See Section I.B.2, *supra*.]

Telemedicine abortion further distances women from the practitioners responsible for caring for them, and approval by FDA would further absolve abortion providers of responsibility for the well-being of their patients. Promoting telemedicine abortion to women and adolescent girls in rural areas with limited access to healthcare is extremely dangerous—they will have little recourse if they face known and predictable emergency complications such as severe hemorrhage.<sup>89</sup>

Nonetheless, Gynuity Health Projects and researchers from UCSF obtained approval from FDA through Investigational New Drug Applications (INDs) to conduct studies that *do not* comply with the Mifeprex REMS. They will use the results of these studies to press for the elimination of the Mifeprex REMS.

#### **a. The “TelAbortion” Direct-to-Consumer Mifeprex Study**

Gynuity Health Projects is the sponsor of the study “Feasibility of Medical Abortion by Direct-to-Consumer Telemedicine.”<sup>90</sup> Gynuity filed an IND with the FDA.<sup>91</sup> The status is listed as “recruiting,” with age eligibility that includes 11-year-old children and an estimated enrollment of 1,000 participants at five locations.<sup>92</sup> The start date is listed as March 22, 2016, and the estimated completion date was extended from June 2018 to June 2019.

The study’s brief summary states: “This pilot study is designed to obtain preliminary data on the safety, acceptability, and feasibility of direct-to-consumer telemedicine

<sup>87</sup> Harrison & Norton Testimony, p. 2.

<sup>88</sup> ACOG Practice Bulletin 181: *Prevention of Rh D Alloimmunization* (Aug. 2017); and SOGC Clinical Practice Guidelines: *Prevention of Rh Alloimmunization* (No. 133, Sept. 2003).

<sup>89</sup> Harrison & Norton Testimony, p. 9.

<sup>90</sup> (NCT02513043), <https://www.clinicaltrials.gov/ct2/show/NCT02513043?term=NCT02513043&rank=1>.

<sup>91</sup> Raymond EG, Chong E, & Hyland P, *Increasing Access to Abortion with Telemedicine*, JAMA Internal Medicine Vol. 176, N. 5 (May 2016).

<sup>92</sup> Hawaii – University of Hawaii Women’s Options Center; Maine – Maine Family Planning; New York – Choices Women’s Medical Center (active, but not recruiting according to ClinicalTrials.gov, and not listed on TelAbortion.org); Oregon and Washington – Planned Parenthood Columbia Willamette; Oregon Health and Sciences University Women’s Health Research Unit. Washington State patients may also participate because an Oregon abortion provider is also licensed in Washington State. Claire Lampen, *Webcam Abortion Services Offer Crucial Access—So What’s Stopping them?* Gizmodo (Apr. 17, 2018).

abortion.”<sup>93</sup> The study’s website states that “[a] TelAbortion involves all the same steps and procedures as a regular medical abortion, but you do them without going into an abortion clinic.”<sup>94</sup>

Women who participate in the study have a video “evaluation” with the study abortion provider over the Internet, during which they can ask questions, provide medical history, and learn about the pre-abortion tests that they need. They also electronically sign consent forms for the study. Afterwards, they are required to obtain the tests and direct the reports to be sent to the study provider.

Once a patient is determined eligible, the study provider will send her a package containing Mifeprex and misoprostol, with instructions that she must follow on her own. She is also instructed to have additional tests to verify that the abortion is complete, and later have another consultation with the study provider to review the results.<sup>95</sup>

Obviously, a woman may *not* take the abortion drugs in the manner prescribed, nor obtain the follow-up care that is recommended. With a doctor-patient relationship limited to online chats, she has virtually no accountability or support as she navigates a complicated procedure. The responsibility of the provider of the drugs to follow up with the patient is obviated as well.

#### **b. The Mifeprex through Pharmacy Dispensing Study**

The University of California, San Francisco (UCSF) is the sponsor of the “Alternative Provision of Medication Abortion via Pharmacy Dispensing” study.<sup>96</sup> Daniel Grossman, M.D., with UCSF is listed as the study’s “responsible party.”<sup>97</sup> Like Gynuity, UCSF filed an IND with the FDA to obtain authorization for this study.<sup>98</sup> The status is listed as “recruiting,” with July 2019 as the estimated completion date. The sponsors plan to recruit 300 patients at four study clinic sites and survey 50 pharmacists at associated study pharmacy sites.<sup>99</sup>

<sup>93</sup> NCT02513043, <https://www.clinicaltrials.gov/ct2/show/NCT02513043?term=NCT02513043&rank=1>.

<sup>94</sup> TelAbortion: The Telemedicine Abortion Study: FAQs, <http://telabortion.org/faq/>.

<sup>95</sup> *Id.*

<sup>96</sup> NCT03320057, <https://www.clinicaltrials.gov/ct2/show/NCT03320057?term=NCT03320057&rank=1>; Daniel Grossman, MD, Research Protocol: *Alternative Provision of Medication Abortion via Pharmacy Dispensing*, Version #:1.3 (JUL. 17, 2018) p. 5.

<sup>97</sup> *Id.*

<sup>98</sup> In a May 2018 phone conversation with a contact for the UCSF study, she stated that the study was approved through an IND application with FDA.

<sup>99</sup> Grossman, pp. 5-7; 16-17.

The stated aim of the study is to “investigate the feasibility, acceptability, and effectiveness of pharmacy dispensing of Mifeprex; safety data will also be collected. . . . *The results of this study eventually could lead to changes in the Mifeprex REMS.* . . .”<sup>100</sup>

The sponsors intend to measure “pharmacist satisfaction with dispensing Mifeprex and the proportion of pharmacists who refuse to dispense the medication to patients.” They secondarily intend to assess patient satisfaction, describe clinical outcomes, including effectiveness and adverse events, and compare pharmacists’ knowledge about medication abortion before and after.<sup>101</sup>

Patients enroll at one of the study clinic sites on Day 1, where they choose medication abortion, have an ultrasound if one has not been done, and obtain pre-abortion counseling. They then are prescribed Mifeprex, misoprostol, and anything else necessary to be filled at the associated study pharmacy site.<sup>102</sup> Some patients have serum hCG measured on the day of Mifeprex administration and again around eight days later “to assess for completion of the abortion.”<sup>103</sup> The “follow-up” for patients “may include a follow-up visit or a phone call from clinic staff approximately 7-14 days after the initial visit.”<sup>104</sup> However, as discussed extensively above, a clinician needs to perform an exam to rule out retained tissue—even if the patient has a negative serum hCG. A phone call that “may” be placed, or fail to connect, is not enough.

Notably, “[a]ll except one of [the participating] pharmacies is [sic] located within the same building as the clinic....”<sup>105</sup> While UCSF is using a community pharmacy not affiliated with the University, the other three study clinic sites are using affiliated pharmacies.<sup>106</sup>

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<sup>100</sup> Grossman, p.14 (emphasis added). The sponsors dubiously assert that “pharmacy dispensing could [] help increase the number of clinicians willing and able to provide medication abortion by enabling them to avoid the associated costs and logistical challenges of stocking and dispensing the medication at their facilities.” They reference a survey of Fellows of the American College of Obstetricians and Gynecologists that sought to determine if doctors not presently practicing abortion would prescribe Mifeprex if their patients could obtain the drug at a pharmacy. Fifty-four percent responded to the survey. Seventy-seven percent of respondents *do not* perform abortions and nine percent perform surgical abortions only—of those, 19% said they would prescribe Mifeprex if it could be obtained at a pharmacy, and an additional 18% said they were unsure. Based on this, the sponsors claim “the proportion of obstetrician-gynecologists providing [Mifeprex] would at least double (from 14% to 29%) “if the dispensing restriction in the REMS were removed and physicians could write a prescription for Mifeprex that could be dispensed at a pharmacy.” The fact that 46 percent of the fellows surveyed did not take the time to respond, however, places this conclusion in doubt. *See* Grossman, pp. 12-14.

<sup>101</sup> Grossman, pp. 15-16.

<sup>102</sup> Grossman, p. 23.

<sup>103</sup> Grossman, p. 23.

<sup>104</sup> Grossman, p. 24.

<sup>105</sup> Grossman, p. 20.

<sup>106</sup> Grossman, pp 16-17.

While the rationale for the study states that pharmacy dispensing of Mifeprex could “help facilitate provision of medication abortion through telemedicine,”<sup>107</sup> the sponsors emphasize that the only difference between this study and FDA protocol “is that the patient would obtain the mifepristone directly from the pharmacist, rather than in a clinic facility.”<sup>108</sup> In fact, the schedules for the participating pharmacists are “mapped” to “ensure that trained pharmacists are available to dispense to study participants during business hours.”<sup>109</sup>

The following demonstrates the extensive assistance that the sponsors offer patients in obtaining the drugs from the participating pharmacies:

[The patient] will be told that only a limited number of pharmacies are able to dispense Mifeprex and given information about how to get to the participating pharmacy (as well as the hours during which a participating pharmacist will be working, if needed). If there are any gaps in staffing at the pharmacy, the patient will be notified of the timing of those gaps in coverage before leaving the clinic via the pharmacy directions/handout. If this will be an issue for the patient, a solution will be found at the clinic before the patient leaves or she will not be enrolled in the study. Patients will be told that if they have any problems accessing the medications at the clinic, they should come back to the clinic [where they can obtain Mifeprex].<sup>110</sup>

While this assistance may ensure that the study does not deviate dramatically from FDA protocol, the study *certainly* does not model the experience a patient would have outside of this controlled environment—particularly a patient who obtains Mifeprex through telemedicine and has no physical contact with her prescriber.

The physical proximity of the study pharmacy sites to the study clinic sites, the probable professional associations between participating doctors and pharmacists, and the extensive assistance offered by the clinics to ensure that patients access abortion-inducing drugs at participating pharmacies, raise questions as to whether the study is fundamentally biased and will inaccurately forecast widespread behavior and experiences if the REMS is removed. Therefore, any results of the study cannot provide a justification for permitting pharmacy distribution of Mifeprex, much less abortion through telemedicine.

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<sup>107</sup> Grossman, p. 6.

<sup>108</sup> Grossman, p. 6.

<sup>109</sup> Grossman, p. 18.

<sup>110</sup> Grossman, pp. 19-20.



Further, as discussed below, eliminating the REMS to enable pharmacy dispensing of Mifeprex is only the beginning of a long-term strategy to achieve over-the-counter status for Mifeprex, further diminishing patient care and abortion provider accountability.

### c. Beyond the Current Studies

A recent article by Dr. Grossman and colleagues reveals that they want Mifeprex access extended even beyond the parameters contained in their Pharmacy Dispensing study. They used an online survey to gauge women's "personal interest in and general support for three alternative methods for accessing abortion pills: (1) in advance from a doctor for future use, (2) over-the-counter (OTC) from a drugstore and (3) online without a prescription."<sup>111</sup>

None of the options in the survey require a healthcare provider to provide patient care comparable to even the *inadequate* care provided in the two studies discussed above. Only the first option requires a prescription from a doctor; however, the doctor would not know in advance when his patient actually becomes pregnant and chooses to use the drugs. The survey disingenuously stated that "[m]edication abortion, or the abortion pill, is a safe and effective way to terminate a pregnancy up to 10 weeks," without informing participants of a single risk associated with the regimen.<sup>112</sup>

Further, in a November, 21, 2018 op-ed, Dr. Grossman advocated for providing abortion pills before women are pregnant. He stated:

The idea is simple: Give women abortion pills *before* they need them – “advance provision,” as it’s known – so that they can take them as soon as they discover a pregnancy. Women could get the pills from their gynecologist at the time of their annual exam, say, or the pills could be made available online.<sup>113</sup>

Incredibly, Dr. Grossman stated that he has “few medical concerns about handing out abortion pills in advance.”<sup>114</sup> He asserts that evidence from advance provision research “could strengthen the case for making [abortion-inducing drugs] available without a prescription.”<sup>115</sup>

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<sup>111</sup> Biggs MA, et al, *Support for and interest in alternative models of medication abortion provision among a national probability sample of U.S. women*, Contraception (2018), <https://doi.org/10.1016/j.contraception.2018.10.007>.

<sup>112</sup> See *id.*

<sup>113</sup> Daniel Grossman, *American women should have access to abortion pills before they need them*, Los Angeles Times (Nov. 21, 2018).

<sup>114</sup> *Id.*

<sup>115</sup> *Id.*

In addition to his failure to address all of the dangers posed by abortion-inducing drugs, Dr. Grossman does not acknowledge the risk that women will share their abortion-inducing pills with other women. While an abortion provider may screen his patient for contraindications to Mifeprex, nothing will stop his patient from giving her stored Mifeprex to a friend who is unaware that she is Rh negative, for instance, which poses health risks for future pregnancies (See section I.B.2, *supra*).

In fact, Dr. Grossman's research program has listed a study titled "Alternative Provision of Medication Abortion Via Advance Provision" on ClinicalTrials.gov, with May 2019 listed as the estimated study start date.<sup>116</sup> In the study, patients who are "at risk of unintended pregnancy and with a desire to avoid pregnancy will be assessed by a clinician and provided counseling on pregnancy recognition and testing, as well as how to administer [drug-induced abortion] at home." They will then receive Mifeprex and misoprostol while *not* pregnant. If/when the patient becomes pregnant and wants to take the drugs, she is instructed to contact a study clinician for an "over-the-phone assessment of eligibility" for drug-induced abortion, "including evaluation of contraindications and gestational age" before taking the drugs, and "then attend a follow-up visit with the clinician."<sup>117</sup> However, it is impossible for the study sponsors to truly assess the patient for contraindications, verify gestational age, prevent patients from sharing the drugs with others, or ensure that patients attend a follow-up visit.

In a 2018 Policy Review, the Guttmacher Institute also advocated for lifting the Mifeprex REMS. However, the article did not stop there. The author argues:

[w]hile lifting the REMS on mifepristone would open new possibilities for medication abortion access, stopping there would fall short of realizing the full potential of this method, particularly when it comes to self-managed abortion care. In a self-management model, anyone who needs to terminate a pregnancy would be able to legally access mifepristone and misoprostol without a requirement to see a health care provider or pharmacist first. . . . To fully integrate self-managed medication abortion with existing abortion practices in the United States, misoprostol and mifepristone must first become available without a prescription.<sup>118</sup>

These recent publications demonstrate how abortion advocates will continue to pressure FDA to eliminate the REMS and move towards over-the-counter access for Mifeprex. In spite of the serious risks and contraindications to the Mifeprex regimen, abortion advocates will not rest until Mifeprex is available to all, without a prescription

<sup>116</sup> NCT03829696, <https://clinicaltrials.gov/ct2/show/NCT03829696?term=NCT03829696&rank=1>.

<sup>117</sup> *Id.*

<sup>118</sup> Donovan MK, *Self-Managed Medication Abortion: Expanding the Available Options for U.S. Abortion Care*, Guttmacher Policy Review, vol. 21 (2018).

or mandatory medical management of any kind. The FDA's vigilance in protecting women from such negligence is critically important.

## 2. Mifeprex Prescribers Should be Certified.

The 2016 regimen requires Mifeprex prescribers to be certified as qualified. This is simply common sense—only healthcare providers qualified to prescribe an abortion-inducing drug should do so. The prescriber form attests that the healthcare provider must be able to assess pregnancy duration, diagnose ectopic pregnancy, and provide or refer for surgical intervention if necessary.

Given that drug-induced abortion is contraindicated beyond 10 weeks' gestation and when the pregnancy is not in the uterus, and that *at least* 1 out of 100 women using Mifeprex need surgery,<sup>119</sup> these qualifications are entirely logical. Yet, abortion advocates, ignoring the best interests of their patients, claim such restrictions are onerous.<sup>120</sup>

## CONCLUSION

The Mifeprex REMS with ETASU remains critical for patient safety. Mifeprex carries risks of life-threatening hemorrhage, infection, continued pregnancy, retained tissue, need for emergency surgery, and death. The 2000 regimen provided significantly more protections for patients than the 2016 regimen. FDA should restore and strengthen elements of the Mifeprex regimen and provider requirements, including: limiting Mifeprex use to 49 days' gestation; requiring that Mifeprex be administered only by or under the supervision of a physically present physician; requiring three office visits by a patient who has been prescribed Mifeprex; clarifying that Mifeprex use is contraindicated for patients who do not have convenient access to emergency medical care; expanding mandatory adverse event reporting; and requiring additional studies of Mifeprex use in at-risk populations.

At the very least, FDA should not further erode patient protections. The agency should retain the Mifeprex REMS, and continue limiting the dispensing of Mifeprex to patients in clinics, medical offices, and hospitals, by or under the supervision of a certified prescriber.

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<sup>119</sup> Mifeprex Risk Evaluation and Mitigation Strategy (REMS), [https://www.accessdata.fda.gov/drugsatfda\\_docs/remis/Mifeprex\\_2016-03-29\\_REMS\\_full.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/remis/Mifeprex_2016-03-29_REMS_full.pdf).

<sup>120</sup> Mifeprex REMS Study Group, *Sixteen Years of Overregulation: Time to Unburden Mifeprex*, N Engl. J. Med. 376;8 (Feb. 23, 2017).

### **C. Environmental Impact**

This petition is categorically excluded under 21 C.F.R. § 25.30.

### **D. Economic Impact**

Available upon Commissioner's request, pursuant to 21 C.F.R. §10.30(3).

### **E. Certification**

The undersigned certify, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioners, which are unfavorable to the petition.

**Signature:** /s/ Donna J. Harrison M.D., Executive Director

**Name of petitioner:** American Association of Pro-Life Obstetricians and Gynecologists

**Mailing address:** PO Box 395, Eau Claire, MI 49111-0395

**Telephone number:** (202) 230-0997

**Signature:** /s/ Quentin L. Van Meter, M.D., FCP, President

**Name of petitioner:** American College of Pediatricians

**Mailing address:** PO Box 357190, Gainesville, FL 32635-7190

**Telephone number:** (352) 376-1877

# Exhibit 36

2019 FDA Abbreviated New Drug Application (ANDA)  
Approval Letter to GenBioPro, Inc. (Apr. 11, 2019)





ANDA 091178

## ANDA APPROVAL

(b) (6), (b) (4)  
GenBioPro, Inc.  
(b) (6), (b) (4)  
Attention: (b) (6), (b) (4)

Dear Sir:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on February 3, 2009, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Mifepristone Tablets, 200 mg.

Reference is also made to the complete response letter issued by this office on February 23, 2018, and to any amendments thereafter.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the ANDA is **approved**, effective on the date of this letter. The (b) (6) has determined your Mifepristone Tablets, 200 mg, to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug (RLD), Mifeprex Tablets, 200 mg, of Danco Laboratories, LLC.

Under section 506A of the FD&C Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

### **RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS**

Section 505-1 of the FD&C Act authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. In accordance with section 505-1(i) of the FD&C Act, a drug that is the subject of an ANDA under section 505(j) is subject to certain elements of the REMS required for the applicable listed drug.

The details of the REMS requirements were outlined in our letter dated June 15, 2011. In that letter, you were also notified that pursuant to section 505-1(i) of the FD&C Act, a drug that is the subject of an ANDA and the listed drug it references must use a single, shared system for elements to assure safe use (ETASU), unless FDA waives that requirement.

Your REMS, known as the Mifepristone REMS Program, submitted on May 30, 2017; is approved, and will be posted on the FDA REMS website: <http://www.fda.gov/remis>

The REMS consists of ETASU and an implementation system.

U.S. Food & Drug Administration  
10903 New Hampshire Avenue  
Silver Spring, MD 20993  
[www.fda.gov](http://www.fda.gov)

Your REMS must be fully operational before you introduce Mifepristone Tablets, 200 mg, into interstate commerce.

The Mifepristone REMS uses a single, shared system for the ETASU. This single, shared system REMS Program currently includes the products listed on the FDA REMS website, available at <http://www.fda.gov/remes>. Other products may be added in the future if additional NDAs or ANDAs are approved.

Under section 505-1(g)(2)(C) of the FD&C Act, FDA can require the submission of a REMS assessment if FDA determines an assessment is needed to evaluate whether the REMS should be modified to ensure the benefits of the drug outweigh the risks or to minimize the burden on the healthcare delivery system of complying with the REMS.

We remind you that you must include an adequate rationale to support a proposed REMS modification for the addition, modification, or removal of any goal or element of the REMS, as described in section 505-1(g)(4) of the FD&C Act.

We also remind you that section 505-1(f)(8) of the FD&C Act prohibits holders of an approved covered application from using any element to assure safe use to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

Prominently identify any submission containing a REMS assessment or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

**ANDA 091178 REMS ASSESSMENT**

**NEW SUPPLEMENT FOR ANDA 091178/S-000  
CHANGES BEING EFFECTED IN 30 DAYS  
PROPOSED MINOR REMS MODIFICATION**

*or*

**NEW SUPPLEMENT FOR ANDA 091178/S-000  
PRIOR APPROVAL SUPPLEMENT  
PROPOSED MAJOR REMS MODIFICATION**

*or*

**NEW SUPPLEMENT FOR ANDA 091178/S-000  
PRIOR APPROVAL SUPPLEMENT  
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABELING CHANGES  
SUBMITTED IN SUPPLEMENT XXX**

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

## **REMS REVISION FOR ANDA 091178**

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

### **SUBMISSION OF REMS DOCUMENT IN SPL FORMAT**

In addition to submitting the proposed REMS as described above, you can also submit the REMS document in Structured Product Labeling (SPL) format. If you intend to submit the REMS document in SPL format, include the SPL file with your proposed REMS submission.

For more information on submitting REMS in SPL format, please email [REMSWebsite@fda.hhs.gov](mailto:REMSWebsite@fda.hhs.gov)

### **REPORTING REQUIREMENTS**

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98 and at section 506I of the FD&C Act. The Agency should be advised of any change in the marketing status of this drug or if this drug will not be available for sale after approval. In particular, under section 506I(b) of the FD&C Act, you are required to notify the Agency in writing within 180 days from the date of this letter if this drug will not be available for sale within 180 days from the date of approval. As part of such written notification, you must include (1) the identity of the drug by established name and proprietary name (if any); (2) the ANDA number; (3) the strength of the drug; (4) the date on which the drug will be available for sale, if known; and (5) the reason for not marketing the drug after approval.

### **PROMOTIONAL MATERIALS**

You may request advisory comments on proposed introductory advertising and promotional labeling materials prior to publication or dissemination. Please note that these submissions are voluntary. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert (PI), Medication Guide, and patient PI (as applicable) to:

OPDP Regulatory Project Manager  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion  
5901-B Ammendale Road  
Beltsville, MD 20705

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

You must also submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)].

Form FDA 2253 is available at

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>.

Information and Instructions for completing the form can be found at

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

## **ANNUAL FACILITY FEES**

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions<sup>1</sup> with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1<sup>st</sup> of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the *Federal Register* notice announcing facility fee amounts.

All finished dosage forms (FDFs) or active pharmaceutical ingredients (APIs) manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

## **CONTENT OF LABELING**

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>, that is identical in content to the approved labeling (including the package insert, and any patient package insert and/or Medication Guide that may be required). Information on submitting SPL files using eLIST may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>. The SPL will be accessible via publicly available labeling repositories.

Sincerely yours,

*{See appended electronic signature page}*

(b) (6)

A large rectangular area of the document is redacted with a solid gray fill, obscuring the signature and name of the official.

Center for Drug Evaluation and Research

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<sup>1</sup> Some of these provisions were amended by the Generic Drug User Fee Amendments of 2017 (GDUFA II) (Public Law 115-52, Title III).





(b) (6)

Digitally signed by (b) (6)

Date: 4/11/2019 02:22:21PM

GUID: 54078879000a1b9e15dd31ed6f0343ca

# Exhibit 37

2019 FDA Supplemental Approval Letter to Danco  
Laboratories, LLC (Apr. 11, 2019)



## DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

NDA 020687/S-022

**SUPPLEMENT APPROVAL**

Danco Laboratories, LLC  
(b) (4), (b) (6)

P.O. Box 4816  
New York, NY 10185

Dear (b) (4), (b) (6) :

Please refer to your Supplemental New Drug Application (sNDA) dated November 4, 2015, received November 5, 2015, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Mifeprex (mifepristone) Tablets.

This Prior Approval supplemental new drug application proposes modifications to the approved risk evaluation and mitigation strategy (REMS) for Mifeprex to establish a single, shared system (SSS) REMS for mifepristone products for the medical termination of intrauterine pregnancy and updates to the approved Prescribing Information, Medication Guide, and REMS materials including the Prescriber Agreement and Patient Agreement Forms to incorporate language reflecting the proposed SSS REMS.

**APPROVAL & LABELING**

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

**CONTENT OF LABELING**

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at:

<http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

### **RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS**

The REMS for Mifeprex (mifepristone) Tablets was originally approved on June 8, 2011. The most recent modification was approved on March 29, 2016. The REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS. Your proposed modifications to the REMS establish a SSS REMS for the elements to assure safe use and the implementation system required for the reference listed drug (RLD) Mifeprex and ANDAs referencing Mifeprex, called the Mifepristone REMS Program.

Your proposed modified REMS, submitted on January 25, 2018, and appended to this letter, is approved.

The timetable for submission of assessments of the REMS must be revised to one year from the date of the initial approval of the SSS REMS (04/11/19) and every three years thereafter.

The revised REMS assessment plan must include, but is not limited to, the following:

Both cumulative data from the date of the initial approval of the SSS REMS (04/11/19) and data from the reporting period (i.e., from the preceding Mifeprex REMS assessment cut-off date to the cut-off date for the Mifepristone REMS Program.)

#### **REMS Assessment Plan**

Provide each metric for the current reporting period and cumulative for the RLD and ANDA(s):

1. Number of prescribers enrolled
2. Number of prescribers ordering mifepristone
3. Number of healthcare providers who attempted to order mifepristone who were not enrolled; describe actions taken
4. Number of women exposed to mifepristone
5. Summary and analysis of any program deviations and corrective action taken
6. Based on the information reported, an assessment and analysis of whether the REMS is meeting its goals and whether modifications to the REMS are needed

The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether 1 or more such goals or such elements should be modified.

We remind you that in addition to the REMS assessments submitted according to the timetable in the approved REMS, you must include an adequate rationale to support any proposed REMS modification for the addition, modification, or removal of any of goal or element of the REMS, as described in section 505-1(g)(4) of the FDCA.

We also remind you that you must submit a REMS assessment when you submit any future supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of the FDCA. This assessment should include:

- a) An evaluation of how the benefit-risk profile will or will not change with the new indication;
- b) A determination of the implications of a change in the benefit-risk profile for the current REMS;
- c) *If the new indication for use introduces unexpected risks:* A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.
- d) *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* A statement about whether the REMS was meeting its goals at the time of that the last assessment and if any modifications of the REMS have been proposed since that assessment.
- e) *If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* Provision of as many of the currently listed assessment plan items as is feasible.
- f) *If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rationale to support the modification, including:* Provision of the reason(s) why the proposed REMS modification is necessary, the potential effect on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan necessary to assess the proposed modified REMS. *If you are not proposing REMS modifications, provide a rationale for why the REMS does not need to be modified.*

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous



REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

**NDA 020687 REMS CORRESPONDENCE  
(insert concise description of content in bold capital letters, e.g.,  
UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT  
METHODOLOGY**

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

Prominently identify any submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

**NDA 020687 REMS ASSESSMENT**

**NEW SUPPLEMENT FOR NDA 020687/S-000/ SECONDARY TRACKING  
NUMBER  
CHANGES BEING EFFECTED IN 30 DAYS  
PROPOSED MINOR REMS MODIFICATION**

*Or*

**NEW SUPPLEMENT FOR NDA 020687/S-000/ SECONDARY TRACKING  
NUMBER  
PRIOR APPROVAL SUPPLEMENT  
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABEL  
CHANGES SUBMITTED IN SUPPLEMENT XXX**

*Or*

**NEW SUPPLEMENT (NEW INDICATION FOR USE)  
FOR NDA 020687/S-000  
REMS ASSESSMENT  
PROPOSED REMS MODIFICATION (if included)**

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page

of the submission:

### **REMS REVISIONS FOR NDA 020687**

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

### **SUBMISSION OF REMS DOCUMENT IN SPL FORMAT**

FDA can accept the REMS document in Structured Product Labeling (SPL) format. If you intend to submit the REMS document in SPL format, as soon as possible, but no later than 14 days from the date of this letter, submit the REMS document in SPL format using the FDA automated drug registration and listing system (eLIST).

For more information on submitting REMS in SPL format, please email [REMS\\_Website@fda.hhs.gov](mailto:REMS_Website@fda.hhs.gov).

### **REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

### **REPORTING REQUIREMENTS**

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call

(b) (6)

Sincerely,

*{See appended electronic signature page}*

(b) (6)

Center for Drug Evaluation and Research

ENCLOSURES:

Content of Labeling  
Prescribing Information  
Medication Guide  
REMS

$/s/$

(b) (6)

04/11/2019 02:13:59 PM

# Exhibit 38

2020 Letter from Am. Coll. of Obstetricians &  
Gynecologists and Soc'y for Maternal-Fetal Med., to  
FDA about Mifepristone REMS (Apr. 20, 2020)





The American College of  
Obstetricians and Gynecologists  
WOMEN'S HEALTH CARE PHYSICIANS



Society for  
Maternal • Fetal  
Medicine  
High-risk pregnancy experts

April 20, 2020

Stephen M. Hahn, M.D.  
Commissioner  
U.S. Food and Drug Administration  
10903 New Hampshire Avenue NW  
Silver Spring, MD 20993

Re: Docket Number: FDA-2020-D-1106; Policy for Certain REMS Requirements During the COVID-19 Public Health Emergency Guidance for Industry and Health Care Professionals

Dear Commissioner Hahn:

On behalf of more than 60,000 of the nation's primary care obstetrician-gynecologists and subspecialty and high-risk obstetric practitioners dedicated to advancing women's health, thank you for your recent action to suspend enforcement of Risk Evaluation and Mitigation Strategy (REMS) requirements for certain drugs with laboratory testing or imaging requirements for the duration of the COVID-19 public health emergency. The American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine urge the U.S. Food and Drug Administration (FDA) to immediately expand this policy to REMS and Elements to Assure Safe Use (ETASU) requirements for certain prescription drugs requiring in-person health care professional administration, where treatment could safely occur through telehealth or self-administration. In addition, physicians who provide such services in accordance with current clinical guidelines during this pandemic should not be held liable.

Obstetrician-gynecologists are serving on the front lines responding to the COVID-19 crisis. In order to provide the safest care for their patients and themselves, in-person visits are limited to emergency and essential physically necessary visits. We support the FDA's acknowledgment that REMS-required health care professional in-person dispensation is difficult because patients may need to avoid public places and patients suspected of having COVID-19 may be self-isolating and/or subject to quarantine. Under these circumstances, undergoing in-person clinic administration in order to obtain a drug subject to a REMS can put patients and others, including health care professionals and their families, at risk for COVID-19 transmission. As referenced in ACOG Committee Opinion #798, *Implementing Telehealth in Practice*, evidence suggests that telehealth provides comparable health outcomes when compared with traditional methods of health care delivery without compromising the patient-physician relationship.<sup>1</sup> Telehealth has quickly become integrated into nearly every aspect of obstetrics and gynecology. During this pandemic, it is essential to use telehealth services to limit COVID-19 transmission.

It is critical that the FDA promptly expand its recent policy to apply to the REMS and ETASU requirements for certain drugs requiring in-person dispensation, especially mifepristone. The current REMS and ETASU requirements for mifepristone are outdated and serve as a barrier to accessing this safe, effective medication. Further, they cause unnecessary delays in obtaining time-sensitive health care, without supporting improvements to patient safety or outcomes. During this federally declared public health emergency, these antiquated and superfluous requirements put patients and their physicians at risk, with no demonstrated benefit. As noted in the ACOG Position Statement, *Improving Access to*

*Mifepristone for Reproductive Health Indications*, mifepristone has been used by over 3 million women in the United States since FDA approval in 2000 and strong evidence exists regarding the safety of mifepristone for medication-induced abortion and medical management of early pregnancy loss.<sup>2,3,4,5</sup>

Restricting access to mifepristone interferes with the ability of obstetrician–gynecologists and other women’s health clinicians to deliver the highest quality care for their patients, especially during the COVID-19 pandemic. Abortion is an essential component of comprehensive health care and is a time-sensitive service for which a delay of several weeks, or in some cases days, may increase the risks or potentially make it completely inaccessible.<sup>6</sup> Temporarily waiving REMS and ETASU requirements that certain drugs be dispensed in-person by certain medical professionals is particularly important for patients who suffer from other medical conditions and are at higher risk of serious complications from COVID-19, as well as those in rural areas for whom hours of travel for in-person administration would disallow social distancing recommendations and travel advisories.

In addition, we urge you to consider waiving the requirement for health care professional administration of subcutaneous depot medroxyprogesterone acetate (DMPA). Several studies have shown patient interest in self-administration and increased continuation of DMPA via subcutaneous at-home delivery.<sup>7,8,9</sup> In a period when limiting patient interactions with the health care system is essential to prevent COVID-19 transmission, it is in our patients’ best interest to have unencumbered access to the contraceptive method of their choice, including DMPA.

Ensuring the safety of patients and physicians during the COVID-19 pandemic requires policy changes such as those already enacted by FDA to waive the REMS requirements for certain drugs with laboratory testing or imaging requirements. We strongly urge FDA to further protect patients and their health care professionals from the risk of transmission by promptly expanding the existing policy to waive REMS and ETASU requirements that certain drugs be dispensed in-person by certain medical professionals. Thank you for your consideration. We are available to answer any questions you may have regarding these issues.

Sincerely,



Maureen G. Phipps, MD, MPH, FACOG  
Chief Executive Officer  
American College of Obstetricians and  
Gynecologists



Judette Louis, MD, MPH  
President  
Society for Maternal-Fetal Medicine



Matt J. Granato, LL.M., MBA  
Chief Executive Officer  
Society for Maternal-Fetal Medicine

<sup>1</sup> Implementing telehealth in practice. ACOG Committee Opinion No. 798. American College of Obstetricians and Gynecologists. *Obstet Gynecol* 2020;135:e73–9.

<sup>2</sup> Improving Access to Mifepristone for Reproductive Health Indications. Position Statement. American College of Obstetricians and Gynecologists. June 2018. Available at <https://www.acog.org/clinical-information/policy-and-position-statements/position-statements/2018/improving-access-to-mifepristone-for-reproductive-health-indications>.

<sup>3</sup> Cleland K, Smith N. Aligning mifepristone regulation with evidence: Driving policy change using 15 years of excellent safety data. *Contraception*. 2015;92(3):179-181. doi:10.1016/j.contraception.2015.06.016.

<sup>4</sup> Sixteen Years of Overregulation: Time to Unburden Mifeprex. *N Engl J Med*. 2017;376(8):790-794.

<sup>5</sup> Song LP, Tang SY, Li CL, Zhou LJGYK, Mo XT. Early medical abortion with self-administered low-dose mifepristone in combination with misoprostol. *J Obstet Gynaecol Res*. 2018;44(9):1705-1711. doi:10.1111/jog.13716.

<sup>6</sup> Joint Statement on Abortion Access During the COVID-19 Outbreak. March 18, 2020. Available at <https://www.acog.org/news/news-releases/2020/03/joint-statement-on-abortion-access-during-the-covid-19-outbreak>.

<sup>7</sup> Upadhyay UD, Zlidar VM, Foster DG. Interest in self-administration of subcutaneous depot medroxyprogesterone acetate in the United States. *Contraception*. 2016;94(4):303-313. doi:10.1016/j.contraception.2016.06.006.

<sup>8</sup> Kohn JE, Simons HR, Della Badia L, et al. Increased 1-year continuation of DMPA among women randomized to self-administration: results from a randomized controlled trial at Planned Parenthood. *Contraception*. 2018;97(3):198-204. doi:10.1016/j.contraception.2017.11.009.

<sup>9</sup> Burke HM, Chen M, Buluzi M, et al. Effect of self-administration versus provider-administered injection of subcutaneous depot medroxyprogesterone acetate on continuation rates in Malawi: a randomised controlled trial. *Lancet Glob Heal*. 2018;6(5):e568-e578. doi:10.1016/S2214-109X(18)30061-5.

# Exhibit 39

2021 FDA Letter to Am. Coll. of Obstetricians &  
Gynecologists and Soc'y for Maternal-Fetal Med. about  
Mifepristone REMS (Apr. 12, 2021)



April 12, 2021

Maureen G. Phipps, MD, MPH, FACOG  
Chief Executive Officer  
American College of Obstetricians and Gynecologists  
c/o Rachel Tetlow, Federal Affairs Director  
[rtetlow@acog.org](mailto:rtetlow@acog.org)

Skye Perryman, General Counsel  
[sperryman@acog.org](mailto:sperryman@acog.org)

William Grobman, MD, MBA  
President  
Society for Maternal-Fetal Medicine  
[w-grobman@northwestern.edu](mailto:w-grobman@northwestern.edu)

Dear Drs. Phipps and Grobman,

In your letter of April 20, 2020, to former Commissioner Stephen Hahn, you expressed concerns about the in-person dispensing requirements for certain prescription drugs during the current public health emergency. In my letter to you of March 19, 2021, I indicated that staff in the Food and Drug Administration's (FDA) Center for Drug Evaluation and Research (CDER) were evaluating the issues you raised.

Following up on my March 19, 2021, letter I am writing to report the results of CDER's review and analysis.

CDER conducted a literature search for studies pertinent to the in-person dispensing requirement in the Mifepristone REMS Program during the COVID-19 pandemic. Based on this literature search, CDER identified four publications that included relevant clinical outcome data.<sup>1</sup> CDER

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<sup>1</sup> Chong E, et al. Expansion of a Direct-to-Patient Telemedicine Abortion Service in the United States and Experience during the COVID-19 Pandemic. *Contraception* 2021 (accepted manuscript). <https://www.sciencedirect.com/science/article/pii/S0010782421000913>; Kerestes C, et al. Provision of medication abortion in Hawai'i during COVID-19: Practical experience with multiple care delivery models. *Contraception* 2021 (accepted manuscript). <https://doi.org/10.1016/j.contraception.2021.03.025>; Aiken A et al. Effectiveness, Safety and Acceptability of No-test Medical Abortion Provided Via Telemedicine: a National Cohort Study. *British J Obstet Gynecol* 2021. <https://obgyn.onlinelibrary.wiley.com/doi/10.1111/1471-0528.16668>; Reynolds-Wright JJ et al. Telemedicine medical abortion at home under 12 weeks' gestation: a prospective observational cohort study during the COVID-19 pandemic. *BMJ Sex Reprod Health* 2021. <https://srh.bmj.com/content/early/2021/02/04/bmj.srh-2020-200976>



found that although there are limitations to the study designs, the overall findings from these studies do not appear to show increases in serious safety concerns (such as hemorrhage, ectopic pregnancy, or surgical interventions) occurring with medical abortion as a result of modifying the in-person dispensing requirement during the COVID-19 pandemic.

CDER also reviewed postmarketing adverse events that reportedly occurred from January 27, 2020 - January 12, 2021, with mifepristone use for medical termination of early pregnancy, along with available information about deviations or noncompliance events associated with the Mifepristone REMS Program.<sup>2</sup> CDER found that the small number of adverse events reported to FDA during the COVID-19 public health emergency (PHE) provide no indication that any program deviation or noncompliance with the Mifepristone REMS Program contributed to the reported adverse events.

In summary, provided the other requirements of the Mifepristone REMS Program are met, and given that the in-person dispensing of mifepristone for medical termination of early pregnancy may present additional COVID-related risks to patients and healthcare personnel because it may involve a clinic visit solely for this purpose, CDER intends to exercise enforcement discretion during the COVID-19 PHE with respect to the in-person dispensing requirement of the Mifepristone REMS Program, including any in-person requirements that may be related to the Patient Agreement Form. Further, to the extent all of the other requirements of the Mifepristone REMS Program are met, CDER intends to exercise enforcement discretion during the COVID-19 PHE with respect to the dispensing of mifepristone through the mail either by or under the supervision of a certified prescriber, or through a mail-order pharmacy when such dispensing is done under the supervision of a certified prescriber.

CDER is communicating this decision to the approved application holders subject to the Mifepristone REMS Program.

Sincerely yours,



Janet Woodcock, M.D.  
Acting Commissioner of Food and Drugs

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<sup>2</sup> See Mifepristone REMS Program at <https://www.accessdata.fda.gov/scripts/cder/remis/index.cfm?event=RemisDetails.page&REMS=390>. CDER's analysis covers both products that are subject to the Mifepristone REMS Program (Mifeprex and the approved generic, Mifepristone Tablets, 200 mg).

# Exhibit 40

2021 FDA Supplemental Approval Letter to Danco  
Laboratories, LLC (May 14, 2021)



NDA 020687/S-024

## SUPPLEMENT APPROVAL

Danco Laboratories LLC

(b) (4), (b) (6)

P.O. Box 4816  
New York, NY 10185

Dear (b) (4), (b) (6) :

Please refer to your supplemental new drug application (sNDA) dated and received March 15, 2021, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Mifeprex (mifepristone) Tablets.

This Changes Being Effected sNDA provides for changes to the single, shared system risk evaluation and mitigation strategy (REMS) for mifepristone products for the medical termination of intrauterine pregnancy, known as the Mifepristone REMS Program, to include gender neutral language in the Patient Agreement Form. This sNDA also provides for minor changes to the REMS document to be consistent with the changes made to the Patient Agreement Form.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter.

### **REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

### **RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS**

The REMS for Mifeprex was originally approved on August 7, 2012, and the most recent REMS modification, establishing the Mifepristone REMS Program, was approved on April 11, 2019. The Mifepristone REMS Program consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS. Your proposed modification to the Mifepristone REMS Program consists of a

NDA 020687/S-024

Page 2

revised Patient Agreement Form to include gender neutral language and minor revisions to the REMS document to be consistent with the revisions to the Patient Agreement Form.

The timetable for submission of assessments of the REMS remains the same as that approved on April 11, 2019.

There are no changes to the REMS assessment plan described in our April 11, 2019 letter.

We remind you that in addition to the REMS assessments submitted according to the timetable in the approved Mifepristone REMS Program, you must include an adequate rationale to support a proposed REMS modification for the addition, modification, or removal of any goal or element of the Mifepristone REMS Program, as described in section 505-1(g)(4) of the FDCA.

We also remind you that you must submit a REMS assessment when you submit a supplemental application for a new indication for use, as described in section 505-1(g)(2)(A) of the FDCA. This assessment should include:

- a) An evaluation of how the benefit-risk profile will or will not change with the new indication;
- b) A determination of the implications of a change in the benefit-risk profile for the current REMS;
- c) *If the new indication for use introduces unexpected risks:* A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.
- d) *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* A statement about whether the REMS was meeting its goals at the time of that last assessment and if any modifications of the REMS have been proposed since that assessment.
- e) *If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* Provision of as many of the currently listed assessment plan items as is feasible.
- f) *If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rationale to support the modification, including:* Provision of the reason(s) why the proposed REMS modification is necessary, the potential effect on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the

**U.S. Food and Drug Administration**  
Silver Spring, MD 20993  
[www.fda.gov](http://www.fda.gov)

NDA 020687/S-024

Page 3

health care delivery system; and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan necessary to assess the proposed modified REMS. *If you are not proposing REMS modifications*, provide a rationale for why the REMS does not need to be modified.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

**NDA 020687 REMS ASSESSMENT METHODOLOGY  
(insert concise description of content in bold capital letters, e.g.,  
ASSESSMENT METHODOLOGY, PROTOCOL, SURVEY METHODOLOGIES,  
AUDIT PLAN, DRUG USE STUDY)**

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

Prominently identify any submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

**NDA 020687 REMS ASSESSMENT**

*or*

**NEW SUPPLEMENT FOR NDA 020687/S-000  
CHANGES BEING EFFECTED IN 30 DAYS  
PROPOSED MINOR REMS MODIFICATION**

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NDA 020687/S-024

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*or*

**NEW SUPPLEMENT FOR NDA 020687/S-000  
PRIOR APPROVAL SUPPLEMENT  
PROPOSED MAJOR REMS MODIFICATION**

*or*

**NEW SUPPLEMENT FOR NDA 020687/S-000  
PRIOR APPROVAL SUPPLEMENT  
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABELING  
CHANGES SUBMITTED IN SUPPLEMENT XXX**

*or*

**NEW SUPPLEMENT (NEW INDICATION FOR USE)  
FOR NDA 020687/S-000/  
REMS ASSESSMENT  
PROPOSED REMS MODIFICATION (if included)**

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

**REMS REVISIONS FOR NDA 020687**

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, or website screenshots are only in PDF format, they may be submitted as such, but Word format is preferred.

**SUBMISSION OF REMS DOCUMENT IN SPL FORMAT**

FDA can accept the REMS document in Structured Product Labeling (SPL) format. If you intend to submit the REMS document in SPL format, as soon as possible, but no later than 14 days from the date of this letter, submit the REMS document in SPL format using the FDA automated drug registration and listing system (eLIST).

For more information on submitting REMS in SPL format, please email [FDAREMSwebsite@fda.hhs.gov](mailto:FDAREMSwebsite@fda.hhs.gov).

**REPORTING REQUIREMENTS**

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

**U.S. Food and Drug Administration**  
Silver Spring, MD 20993  
[www.fda.gov](http://www.fda.gov)

NDA 020687/S-024

Page 5

If you have any questions, call (b) (6).

Sincerely,

*{See appended electronic signature page}*

(b) (6)

Center for Drug Evaluation and Research

ENCLOSURE:

- REMS

**U.S. Food and Drug Administration**  
Silver Spring, MD 20993  
[www.fda.gov](http://www.fda.gov)

-----  
**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**  
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/s/  
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(b) (6)

05/14/2021 02:14:29 PM

# Exhibit 41

2021 Updated REMS Mifepristone Tablets,  
200 mg (May 14, 2021)

Initial Shared System REMS approval: 04/2019  
Most Recent Modification: 05/2021

Mifepristone Tablets, 200 mg

Progestin Antagonist

## RISK EVALUATION AND MITIGATION STRATEGY (REMS) SINGLE SHARED SYSTEM FOR MIFEPRISTONE 200MG

### I. GOAL

The goal of the REMS for mifepristone is to mitigate the risk of serious complications associated with mifepristone by:

- a) Requiring healthcare providers who prescribe mifepristone to be certified in the Mifepristone REMS Program.
- b) Ensuring that mifepristone is only dispensed in certain healthcare settings by or under the supervision of a certified prescriber.
- c) Informing patients about the risk of serious complications associated with mifepristone.

### II. REMS ELEMENTS

#### A. Elements to Assure Safe Use

1. Healthcare providers who prescribe mifepristone must be specially certified.
  - a. To become specially certified to prescribe mifepristone, healthcare providers must:
    - i. Review the Prescribing Information for mifepristone.
    - ii. Complete a *Prescriber Agreement Form*. By signing a *Prescriber Agreement Form*, prescribers agree that:
      - 1) They have the following qualifications:
        - a) Ability to assess the duration of pregnancy accurately
        - b) Ability to diagnose ectopic pregnancies
        - c) Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or to have made plans to provide such care through others, and ability to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.
      - 2) They will follow the guidelines for use of mifepristone (see b.i-v below).
  - b. As a condition of certification, healthcare providers must follow the guidelines for use of mifepristone described below:
    - i. Review the *Patient Agreement Form* with the patient and fully explain the risks of the mifepristone treatment regimen. Answer any questions the patient may have prior to receiving mifepristone.



- ii. Sign the *Patient Agreement Form* and obtain the Patient's signature on the *Form*
  - iii. Provide the patient with a copy of the *Patient Agreement Form* and Medication Guide.
  - iv. Place the signed *Patient Agreement Form* in the patient's medical record.
  - v. Record the serial number from each package of mifepristone in each patient's record.
  - vi. Report any deaths to the Mifepristone Sponsor that provided the mifepristone, identifying the patient by a non-identifiable reference and the serial number from each package of mifepristone.
- c. Mifepristone Sponsors must:
- i. Ensure that healthcare providers who prescribe their mifepristone are specially certified in accordance with the requirements described above and de-certify healthcare providers who do not maintain compliance with certification requirements
  - ii. Provide the Prescribing Information and their *Prescriber Agreement Form* to healthcare providers who inquire about how to become certified.

The following materials are part of the REMS and are appended:

- *Prescriber Agreement Form for Danco Laboratories, LLC*
  - *Prescriber Agreement Form for GenBioPro, Inc.*
  - *Patient Agreement Form*
2. Mifepristone must be dispensed to patients only in certain healthcare settings, specifically clinics, medical offices, and hospitals, by or under the supervision of a certified prescriber.
    - a. Mifepristone Sponsors must:
      - i. Ensure that their mifepristone is available to be dispensed to patients only in clinics, medical offices and hospitals by or under the supervision of a certified prescriber.
      - ii. Ensure that their mifepristone is not distributed to or dispensed through retail pharmacies or other settings not described above.
  3. Mifepristone must be dispensed to patients with evidence or other documentation of safe use conditions.
    - a. The patient must sign a *Patient Agreement Form* indicating that the patient has:
      - i. Received, read and been provided a copy of the *Patient Agreement Form*.
      - ii. Received counseling from the prescriber regarding the risk of serious complications associated with mifepristone.

## B. Implementation System

1. Mifepristone Sponsors must ensure that their mifepristone is only distributed to clinics, medical offices and hospitals by or under the supervision of a certified prescriber by:
  - a. Ensuring that distributors who distribute their mifepristone comply with the program requirements for distributors. The distributors must:

- i. Put processes and procedures in place to:
    - a. Complete the healthcare provider certification process upon receipt of a Prescriber Agreement Form.
    - b. Notify healthcare providers when they have been certified by the Mifepristone REMS Program.
    - c. Ship mifepristone only to clinics, medical offices, and hospitals identified by certified prescribers in their signed *Prescriber Agreement Form*.
    - d. Not ship mifepristone to prescribers who become de-certified from the Mifepristone REMS Program.
    - e. Provide the Prescribing Information and their Prescriber Agreement Form to healthcare providers who (1) attempt to order mifepristone and are not yet certified, or (2) inquire about how to become certified.
  - ii. Put processes and procedures in place to maintain a distribution system that is secure, confidential and follows all processes and procedures, including those for storage, handling, shipping, tracking package serial numbers, proof of delivery and controlled returns of mifepristone.
  - iii. Train all relevant staff on the Mifepristone REMS Program requirements.
  - iv. Comply with audits by Mifepristone Sponsors, FDA or a third party acting on behalf of Mifepristone Sponsors or FDA to ensure that all processes and procedures are in place and are being followed for the Mifepristone REMS Program. In addition, distributors must maintain appropriate documentation and make it available for audits.
- b. Ensuring that distributors maintain secure and confidential distribution records of all shipments of mifepristone.
2. Mifepristone Sponsors must monitor their distribution data to ensure compliance with the REMS Program.
  3. Mifepristone Sponsors must audit their new distributors within 90 calendar days after the distributor is authorized to ensure that all processes and procedures are in place and functioning to support the requirements of the Mifepristone REMS Program. Mifepristone Sponsors will take steps to address their distributor compliance if noncompliance is identified.
  4. Mifepristone Sponsors must take reasonable steps to improve implementation of and compliance with the requirements of the Mifepristone REMS Program based on monitoring and assessment of the Mifepristone REMS Program.
  5. Mifepristone Sponsors must report to FDA any death associated with mifepristone whether or not considered drug-related, as soon as possible but no later than 15 calendar days from the initial receipt of the information by the applicant. This requirement does not affect the applicants other reporting and follow-up requirements under FDA regulations.

### **C. Timetable for Submission of Assessments**

The NDA Sponsor must submit REMS assessments to FDA one year from the date of the initial approval of the REMS (04/11/2019) and every three years thereafter. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 calendar days before the submission date for that assessment. The NDA Sponsor must submit each assessment so that it will be received by the FDA on or before the due date.

# Exhibit 42

2021 FDA Center for Drug Evaluation and Research  
Director Patrizia Cavazzoni Letter to Dr. Graham  
Chelius (Dec. 16, 2021)

## Food and Drug Administration

EX. 42 pg. 01  
MPI App. 728

# Exhibit 43

2021 FDA Letter to Am. Ass'n of Pro-Life Obstetricians  
& Gynecologists and Am. Coll. of Pediatricians denying  
in part and granting in part 2019 Citizen Petition,  
Docket No. FDA-2019-P-1534 (Dec. 16, 2021) (2019  
Petition Denial)





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December 16, 2021

Re: Docket No. FDA-2019-P-1534

Dear Drs. Harrison and Van Meter:

This letter responds to your citizen petition submitted to the Food and Drug Administration (FDA or Agency) on March 29, 2019, on behalf of the American Association of Pro-Life Obstetricians and Gynecologists and the American College of Pediatricians (Petition). In the Petition, you request that FDA: (1) restore and strengthen elements of the Mifeprex regimen and prescriber requirements approved in 2000, and (2) retain the Mifeprex Risk Evaluation and Mitigation Strategy (REMS) and continue limiting the dispensing of Mifeprex to patients in clinics, medical offices, and hospitals, by or under the supervision of a certified prescriber.

Specifically, in your Petition you request that the Agency:

(1) Restore and strengthen elements of the Mifeprex regimen and prescriber requirements approved in 2000, to include the following:

- Indications and Usage - Mifeprex, in a regimen with misoprostol, for the termination of intrauterine pregnancy, should be limited to 49 days gestation.
- Dosage and Administration:
  - Mifeprex should be administered by or under the supervision of a physically present and certified physician who has ruled out ectopic pregnancy.
  - The use of Mifeprex and misoprostol for the termination of pregnancy should require three office visits by the patient.

U.S. Food & Drug Administration  
10903 New Hampshire Avenue  
Silver Spring, MD 20993  
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- Contraindications - Mifeprex use is contraindicated for patients who do not have convenient access to emergency medical care.
  - Adverse Event Reporting - Certified prescribers, emergency medical personnel, physicians treating complications, and Danco Laboratories should report to FDA's MedWatch Reporting system any deaths, hospitalizations, blood transfusions, emergency room visits, failures requiring surgical completion, ongoing pregnancy, or other major complications following the use of Mifeprex and misoprostol.
  - Additional studies - The Mifeprex REMS should require a formal study of outcomes for at-risk populations, including: patients under the age of 18; patients with repeat Mifeprex abortions; patients who have limited access to emergency room services; and patients who self-administer misoprostol.
- (2) Retain the Mifeprex REMS and continue limiting the dispensing of Mifeprex to patients in clinics, medical offices, and hospitals, by or under the supervision of a certified prescriber.

We have carefully considered the information submitted in your Petition and other relevant data available to the Agency. Based on our review of this information, your Petition is granted in part and denied in part.

## **I. BACKGROUND**

### **A. Mifeprex**

On September 28, 2000, FDA approved Mifeprex for the medical termination of intrauterine pregnancy through 49 days' pregnancy (new drug application (NDA) 020687). The application was approved under part 314, subpart H (21 CFR part 314, subpart H), "Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses" (subpart H). Specifically, § 314.520 of subpart H provides for approval with restrictions that are needed to assure the safe use of the drug product. In accordance with § 314.520, FDA restricted the distribution of Mifeprex as specified in the September 2000 approval letter.<sup>1</sup>

Subsequently, Mifeprex was identified as one of the products that was deemed to have in effect an approved REMS under the Food and Drug Administration Amendments Act of 2007 (FDAAA) because on the effective date of Title IX, subtitle A of FDAAA (March 28, 2008), Mifeprex had in effect elements to assure safe use.<sup>2</sup> Accordingly, in June 2011, we approved a REMS for Mifeprex, consisting of a Medication Guide, elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments of the REMS.

Elements to assure safe use included: (1) prescriber certification (ETASU A); (2) that Mifeprex is dispensed only in certain healthcare settings by or under the supervision of a certified prescriber

<sup>1</sup> See [https://www.accessdata.fda.gov/drugsatfda\\_docs/appltr/2000/20687appltr.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/appltr/2000/20687appltr.pdf).

<sup>2</sup> 73 FR 16313 (Mar. 27, 2008).

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(ETASU C); and (3) that Mifeprex is dispensed only with documentation of safe use conditions (ETASU D). Documentation of safe use conditions consists of a Patient Agreement Form between the prescriber and the patient indicating that the patient has received counseling from the prescriber regarding the risk of serious complications associated with Mifeprex.

On March 29, 2016, we approved an efficacy supplement (S-020) to NDA 020687 for Mifeprex submitted by the applicant Danco Laboratories, LLC (S-020 efficacy supplement). The approval included changes in the dose of Mifeprex and the dosing regimen for taking Mifeprex and misoprostol (including the dose of misoprostol and a change in the route of misoprostol administration from oral to buccal (in the cheek pouch); the interval between taking Mifeprex and misoprostol; and the location at which the patient may take misoprostol). The approval also modified the gestational age up to which Mifeprex has been shown to be safe and effective, as well as the process for follow-up after administration of the drug.

Specifically, the following changes, among others, were made as part of the 2016 approval:<sup>3</sup>

- Revised the dosing regimen to consist of 200 mg of Mifeprex taken by mouth, followed in 24-48 hours by 800 mcg of misoprostol taken buccally (in the cheek pouch). This differs from the originally approved dosing regimen of 600 mg of oral Mifeprex followed 48 hours later by 400 mcg of oral misoprostol.
- Revised the indication for use of Mifeprex, in a regimen with misoprostol, to extend the maximum gestational age for the medical termination of intrauterine pregnancy from 49 days to 70 days.
- Reduced the number of office visits by the patient under the approved regimen from three to one.
- Replaced the term “physician” with the term “healthcare provider.”

In addition, after reviewing the data and information submitted by the applicant in the S-020 efficacy supplement, and after taking into consideration the safety data that had become available since the initial approval of Mifeprex in 2000, we determined the Mifeprex REMS continued to be necessary to ensure the benefits of the product outweigh the risks. However, we approved modifications to the Mifeprex REMS that reflected the changes approved in the efficacy supplement. These changes to the REMS included, among others:<sup>4</sup>

- Updating the Prescriber Agreement Form to reflect the revised indication and dosing regimen.
- Removing the Medication Guide as a REMS element (but retaining the Medication Guide as labeling).

<sup>3</sup> See [https://www.accessdata.fda.gov/drugsatfda\\_docs/appletter/2016/020687Orig1s020ltr.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2016/020687Orig1s020ltr.pdf) and [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2016/020687s020lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020687s020lbl.pdf).

<sup>4</sup> See [https://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2016/020687Orig1s020RemsR.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/020687Orig1s020RemsR.pdf).

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- Removing the requirement that certified prescribers report certain enumerated adverse events to the applicant (specifically, any hospitalization, transfusion or other serious adverse events), but retaining the requirement that certified prescribers report all deaths to the sponsor.

Under the March 2016 approval, the Mifeprex REMS also continued to require that Mifeprex be dispensed to patients only in certain healthcare settings, specifically, clinics, medical offices, and hospitals, by or under the supervision of a certified prescriber.<sup>5</sup>

## **B. Generic Version of Mifeprex**

On April 11, 2019, we approved GenBioPro, Inc.'s generic version of Mifeprex, Mifepristone Tablets, 200 mg (abbreviated new drug application (ANDA) 091178). This action took place after this Petition was submitted to the Agency. As required by 21 CFR 314.94(a)(8), GenBioPro's approved generic version of Mifeprex, Mifepristone Tablets, 200 mg, has the same labeling (with certain permissible differences) as the brand product it references, Mifeprex. Accordingly, although we refer to the Mifeprex labeling in several sections of this response, our discussions in this response apply equally to both the NDA and the generic product labeling, unless otherwise specifically noted.<sup>6</sup>

GenBioPro's generic version of Mifeprex is subject to the same ETASU as its listed drug (21 U.S.C. -1(i)). At the time we approved GenBioPro's generic version of Mifeprex, that ANDA product was required to use a single, shared system for the ETASU with the brand drug product, Mifeprex, unless the requirement was waived by FDA (21 U.S.C. 355-1(i)). FDA did not waive this requirement. Accordingly, at the same time that FDA approved GenBioPro's generic version of Mifeprex in 2019, FDA approved a supplemental new drug application (sNDA) for Mifeprex, approving modifications to the existing, approved REMS for Mifeprex to establish a single, shared system REMS for mifepristone products for the medical termination of intrauterine pregnancy through 70 days gestation (referred to as the Mifepristone REMS Program). In establishing the single, shared system REMS in 2019, no substantive changes were made to the ETASU in the March 2016 Mifeprex REMS. References to the REMS in this response refer to the Mifepristone REMS Program established in 2019, unless otherwise noted.

## **C. In-Person Dispensing Requirement During the COVID-19 PHE**

<sup>5</sup> See [https://www.accessdata.fda.gov/drugsatfda\\_docs/applletter/2016/020687Orig1s020ltr.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/applletter/2016/020687Orig1s020ltr.pdf).

<sup>6</sup> We note that Korlym and the generic version of Korlym (Mifepristone Tablets, 300 mg) contain the same active ingredient – mifepristone – as Mifeprex and the generic version of Mifeprex (Mifepristone Tablets, 200 mg). Although these drug products contain the same active ingredient, their intended uses target different receptors, and the products have different strengths and use different dosing regimens. Korlym and the generic version of Korlym are approved for the control of hyperglycemia (high blood sugar levels) due to hypercortisolism in adult patients with endogenous Cushing's syndrome who have type 2 diabetes or glucose intolerance, and have failed surgery or are not candidates for surgery. References to mifepristone in this response refer to the use of mifepristone for the medical termination of intrauterine pregnancy through 70 days gestation, unless otherwise noted.

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FDA has recognized that during the COVID-19<sup>7</sup> public health emergency (PHE),<sup>8</sup> certain REMS requirements for various products may be difficult to comply with because patients may need to avoid public places and patients suspected of having COVID-19 may be self-isolating and/or subject to quarantine. The Agency has also received queries concerning products with REMS that have ETASUs, including REMS with ETASUs that restrict distribution, and the impact of such ETASUs on patient access when patients self-isolate or are subject to quarantine.

In April 2021, FDA communicated its intent to exercise enforcement discretion during the COVID-19 PHE regarding the requirement in the Mifepristone REMS Program that mifepristone used for medical termination of intrauterine pregnancy through 70 days gestation be dispensed to patients by or under the supervision of a certified prescriber only in certain healthcare settings, specifically clinics, medical offices, and hospitals (referred to as the “in-person dispensing requirement”).

Specifically, FDA communicated that provided all other requirements of the Mifepristone REMS Program are met, the Agency intends to exercise enforcement discretion with respect to the in-person dispensing requirement of the Mifepristone REMS Program, including any in-person requirements that may be related to the Patient Agreement Form, during the COVID-19 PHE. This determination, which FDA made on April 12, 2021, was effective immediately. We also note that from July 13, 2020 to January 12, 2021, per a court order, FDA was enjoined from enforcing the in-person dispensing requirement of the Mifepristone REMS Program.<sup>9</sup>

Further, and as we also communicated on April 12, 2021, to the extent all of the other requirements of the Mifepristone REMS Program are met, the Agency intends to exercise enforcement discretion during the COVID-19 PHE with respect to the dispensing of Mifeprex or the approved generic version of Mifeprex, Mifepristone Tablets, 200 mg, through the mail, either by or under the supervision of a certified prescriber, or through a mail-order pharmacy when such dispensing is done under the supervision of a certified prescriber.

FDA’s intent to exercise enforcement discretion with respect to these requirements during the COVID-19 PHE was the result of a thorough scientific review by experts within FDA’s Center for Drug Evaluation and Research (CDER), who evaluated relevant information, including available clinical outcomes data and adverse event reports.

#### **D. Minor Modification**

<sup>7</sup> The virus has been named “SARS-CoV-2” and the disease it causes has been named “Coronavirus Disease 2019” (COVID-19).

<sup>8</sup> Secretary of Health and Human Services, Determination that a Public Health Emergency Exists (originally issued Jan. 31, 2020, and subsequently renewed), *available at* <https://www.phe.gov/emergency/news/healthactions/phe/Pages/default.aspx>.

<sup>9</sup> *Am. Coll. of Obstetricians & Gynecologists v. FDA*, 472 F. Supp. 3d 183, 233 (D. Md. July 13, 2020), order clarified, 2020 WL 8167535 (D. Md. Aug. 19, 2020) (preliminarily enjoining FDA from enforcing the in-person dispensing requirement and any other in-person requirements of the Mifepristone SSS REMS); *FDA v. Am. Coll. of Obstetricians & Gynecologists*, 141 S. Ct. 578 (Jan. 12, 2021) (staying the preliminary injunction imposed by the District Court).



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In response to a request submitted by the applicants, FDA approved a minor modification to the Mifepristone REMS Program on May 14, 2021. This minor modification revised the Patient Agreement Form to use gender neutral language. Specifically, the pronouns “she” and “her” in the Patient Agreement Form were replaced with “the patient.” The minor modification also included revisions to the REMS document to be consistent with the revisions to the Patient Agreement Form. These changes did not affect the substance of the Patient Agreement Form, the REMS document, or the Mifepristone REMS Program.

### **E. Review of the Mifepristone REMS Program**

In 2021, FDA also undertook a full review of the Mifepristone REMS Program.<sup>10</sup> In conducting this review, FDA reviewed multiple different sources of information, including published literature, safety information submitted to the Agency during the COVID-19 PHE, FDA Adverse Event Reporting System (FAERS) reports, the first REMS assessment report for the Mifepristone REMS Program, and information provided by advocacy groups, individuals, and the Plaintiffs in ongoing litigation, as well as information submitted by the sponsors of the NDA and the ANDA (together, the Applicants). As discussed in more detail below, based on our review of this information, FDA has determined that certain elements of the Mifepristone REMS Program remain necessary to assure the safe use of mifepristone for medical termination of intrauterine pregnancy through 70 days gestation; and therefore, the Mifepristone REMS Program continues to be necessary to ensure the benefits outweigh the risk. Specifically, we find that the healthcare provider certification and dispensing of mifepristone to patients with evidence or other documentation of safe use conditions continue to be necessary components of the REMS to ensure the benefits of mifepristone outweigh the risks for this indication.

We also find that the in-person dispensing requirement is no longer necessary to assure the safe use of mifepristone for medical termination of intrauterine pregnancy through 70 days gestation. We have concluded that mifepristone will remain safe and effective for medical abortion if the in-person dispensing requirement is removed, provided all the other requirements of the REMS are met and pharmacy certification is added.<sup>11</sup> Removing the in-person dispensing requirement will render the REMS less burdensome to healthcare providers and patients, and provided all other requirements of the REMS are met, including the additional requirement for pharmacy certification, the REMS will continue to ensure that the benefits of mifepristone for medical abortion outweigh the risks. Accordingly, today we are sending a REMS Modification Notification letter to both Applicants in the Mifepristone REMS Program. As stated in that letter, FDA has concluded that a modification is necessary and must include the following changes:

- Removing the requirement that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals.

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<sup>10</sup> We note that the Agency is in litigation regarding the Mifepristone REMS Program and committed to conducting a full review of the Mifepristone REMS Program, including reviewing any relevant data and evidence submitted to the Agency by the Plaintiffs in that litigation (*Chelius et al v. Becerra*, Joint Mot. to Stay Case Pending Agency Review, ECF No. 148, May 7, 2021, Civ. No. 1:17-00493 (D. Haw.)).

<sup>11</sup> Although we have determined that the Mifepristone REMS Program must be modified to add a requirement for pharmacy certification, this was not raised in your Petition and therefore is not discussed further in this response.

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- Adding a requirement that pharmacies that dispense the drug be specially certified.

## II. DISCUSSION OF ISSUES RAISED

### A. Mifeprax Regimen

#### 1. Indications and Usage

In the Petition, you ask FDA to restore and strengthen elements of the Mifeprax regimen and prescriber requirements approved in 2000, to limit Mifeprax, in a regimen with misoprostol, for the termination of intrauterine pregnancy, to 49 days gestation (Petition at 1 and 3). For the reasons explained below, we deny this request.

Citing to a 2011 study and a practice bulletin issued by the American College of Obstetricians and Gynecologists (ACOG), you state that medical abortion<sup>12</sup> regimens demonstrate an increase in complications and failures, including serious risks of hemorrhage, infection, and ongoing pregnancy, after 49 days gestation (Petition at 3-4).

Our review of the S-020 efficacy supplement in 2016 concluded that Mifeprax, in a regimen with misoprostol, is safe and effective for medical termination of intrauterine pregnancy through 70 days gestation.<sup>13</sup> Complete medical abortion rates from the pivotal clinical trials relied on for the initial approval of Mifeprax (with an indication for medical termination of intrauterine pregnancy through 49 days gestation) were 92.1 percent and 95.5 percent in the United States and French trials, respectively.<sup>14</sup> The studies reviewed in support of the 2016 approval for Mifeprax (with an indication for medical termination of intrauterine pregnancy through 70 days gestation) showed comparable efficacy. The 2016 Clinical Review of the S-020 efficacy supplement summarized clinical outcomes and adverse effects from 22 studies (7 in the United States and 15 from outside the United States) through 70 days gestation, using the currently approved regimen of 200 mg oral mifepristone with 800 mcg buccal misoprostol. The ranges of complete medical abortion rates calculated by the clinical reviewer were 93.2 percent to 98.7 percent in the United States studies, and 92 percent to 98 percent in the non-United States studies.<sup>15</sup>

Serious adverse events associated with the use of mifepristone through 70 days gestational age are rare. Per the current mifepristone labeling, the rates of serious adverse events are low: transfusions are 0-0.1 percent, sepsis is less than 0.01 percent, hospitalization related to medical abortion is 0-0.7 percent, and hemorrhage is 0.1 percent.<sup>16</sup> As discussed

<sup>12</sup> In this response, the terms “medical abortion” and “medication abortion” both refer to the use of mifepristone, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy.

<sup>13</sup> See 2016 Clinical Review available at [https://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2016/020687Orig1s020MedR.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/020687Orig1s020MedR.pdf), at 32-38 and 47-47.

<sup>14</sup> See 1999 Medical Officer’s Review, available at [http://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2000/20687\\_Mifepristone\\_medr\\_P1.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/20687_Mifepristone_medr_P1.pdf), at 11 (Table 1) and 16.

<sup>15</sup> See 2016 Clinical Review, supra n. 13, at 28-31.

<sup>16</sup> See [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2019/020687s022lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020687s022lbl.pdf).

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throughout this response, the benefit/risk assessment supported our 2016 conclusion that the product is safe and effective through 70 days gestation.

In support of your assertion that medical abortion demonstrates an increase in complications after 49 days gestation, you cite to Mentula, et al.,<sup>17</sup> a register-based, retrospective cohort study that included 18,248 women in Finland who underwent medical abortion between January 1, 2003, and December 31, 2006 (Petition at 3). As an initial matter, we note that the Mentula study was primarily designed to assess the immediate adverse events following medical abortion in the second trimester (13 to 24 gestational weeks as defined by the authors) and then compare those events to those identified with medical abortion in the first trimester (up to 12 gestational weeks as defined by the authors). The study was not designed to compare rates of complications across gestational weeks within the first trimester. It is true that the Mentula publication includes information on the percentages of women who had surgical evacuation following medical abortion and the percentages of women who had infection following medical abortion, based on weekly gestational age, from 5 weeks to 20 weeks gestation.<sup>18</sup> However, the data in the Mentula study are relatively old (2003-2006); in our 2016 review of the S-020 efficacy supplement, we conducted an extensive review of more recent data<sup>19</sup> and concluded that Mifeprex, in a regimen with misoprostol, is safe and effective for medical termination of intrauterine pregnancy through 70 days gestation.

You also cite to ACOG Practice Bulletin No. 143, which states: “the risk of clinically significant bleeding and transfusion may be lower in women who undergo medical abortion of gestations up to 49 days compared with those who undergo medical abortion of gestations of more than 49 days.”<sup>20</sup> This statement is based on a 1998 publication which evaluated patients undergoing medical abortion with mifepristone 600 mg and then oral misoprostol 400 mcg two days later.<sup>21</sup> The regimen studied in this 1998 publication is not the currently approved regimen for mifepristone in the United States. Further, ACOG Practice Bulletin No. 143 has been withdrawn and replaced by Practice Bulletin No. 225, which was published in October 2020 and no longer contains this statement.<sup>22</sup>

You also state that the failure rate of the approved regimen (which you refer to as the “buccal misoprostol regimen”) increases as the gestational age increases, especially at

<sup>17</sup> Mentula MJ, Niinimäke M, Suhonen S, et al. Immediate Adverse Events After Second Trimester Medical Termination of Pregnancy: Results of a nationwide registry study, *Human Reproduction*. 2011;26(4):927-932.

<sup>18</sup> *Id.* at Fig. 2 and Fig. 3. Surgical intervention after medical abortion and infection after medical abortion are two distinct adverse events. The calculation of abortion completion rates accounts for the need for surgical intervention. In clinical studies we reviewed, success of medical abortion was defined as the complete expulsion of the products of conception without the need for surgical intervention.

<sup>19</sup> See 2016 Cross-Discipline Team Leader Review, available at [https://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2016/020687Orig1s020CrossR.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/020687Orig1s020CrossR.pdf), at 37 (Table 4).

<sup>20</sup> Petition at 3. See Medical Management of First-Trimester Abortion. ACOG Practice Bulletin Number 143. March 2014 (Reaffirmed 2016. Replaces Practice Bulletin Number 67, October 2005); *Obstet Gynecol*. 2014 Mar;123(3):676-692 at 680.

<sup>21</sup> Spitz I, Bardin CW, Benton L, Robbins A. Early pregnancy termination with mifepristone and misoprostol in the United States, *NEJM*. 1998;338 (18):1241-1247.

<sup>22</sup> See ACOG Practice Bulletin No. 225. Medication Abortion Up to 70 Days of Gestation. *Obstetrics and Gynecology* 2020; 136(4); e31 to e47.

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gestational ages greater than 49 days, relying on a 2015 meta-analysis,<sup>23</sup> and that the gestational limit should not have been increased (Petition at 3-4). We agree that the failure rate of medical abortion regimens, including the currently approved regimen, generally increases with increasing gestational age. However, the increase in failure rate with each incremental week of gestation, as described in approved mifepristone labeling and in this 2015 meta-analysis, is small, and we believe that the benefit/risk profile for medical termination of intrauterine pregnancy between 49 and 70 days gestation remains acceptable.

For these reasons, we deny your request that FDA limit mifepristone, in a regimen with misoprostol for the termination of intrauterine pregnancy, to 49 days gestation.

## 2. Dosage and Administration

### a. Prescriber Qualifications

You state that FDA should limit the “ability” to prescribe and dispense Mifeprex to qualified, licensed physicians, rather than permitting non-physicians to apply to be certified prescribers, because of the regimen’s serious risks and because physicians are better trained to diagnose patients who have contraindications to Mifeprex and to verify gestational age (Petition at 4). We do not agree.

Healthcare providers who are licensed to prescribe can become certified in REMS programs if they are able to meet the applicable REMS requirements. To become certified to prescribe mifepristone under the Mifepristone REMS Program, the prescriber must review the prescribing information for mifepristone and complete a Prescriber Agreement Form. By signing the form, the prescriber agrees that they meet certain qualifications, including the ability to date pregnancies accurately and to diagnose ectopic pregnancies. These healthcare providers must also: (1) be able to provide any necessary surgical intervention or have made arrangements for others to provide for such care; or (2) be able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.<sup>24</sup>

In our review of the S-020 efficacy supplement in 2016, we determined that available data support that Mifeprex is safe and effective when prescribed by midlevel providers, such as physician assistants and nurse practitioners, as well as by physicians.<sup>25</sup> Our 2016 review included four studies that evaluated the safety and efficacy of medical abortion when performed by non-physician healthcare providers. Two trials evaluated the currently

<sup>23</sup> Petition at 4, fn. 6 (citing Chen MJ, Creinin MD, *Mifepristone with Buccal Misoprostol for Medical Abortion*, *Obstet. Gynecol* 126 (1) July 2015 12-21).

<sup>24</sup> See [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2019/020687s0221b1.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020687s0221b1.pdf); see also <https://www.accessdata.fda.gov/scripts/cder/remis/index.cfm?event=RemsDetails.page&REMS=390>.

<sup>25</sup> See 2016 Clinical Review, *supra* n. 13, at 79; see also 2016 Cross-Discipline Team Leader Review, *supra* n. 19, at 17-18. We also note that in most states, midlevel clinicians, such as physician assistants and nurse practitioners, are licensed to prescribe medications.

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approved Mifeprex and buccal misoprostol regimen (Olavarrieta and Kopp Kallner),<sup>26,27</sup> one trial studied a regimen using vaginal misoprostol (Warringer);<sup>28</sup> a fourth study did not specify the route of misoprostol administered (Puri).<sup>29</sup> Olavarrieta reported a completion rate of 97.9 percent when medical abortion was provided by nurses as compared with 98.4 percent with physicians. Kopp Kallner reported a completion rate of 99 percent with certified nurse midwives versus 97.4 percent with physicians. Warringer reported an abortion completion rate of 97.4 percent with nurses as compared with 96.3 percent with physicians. Puri reported an abortion completion rate of 96.8 percent when the service was provided by nurse-midwives as compared with 97.4 percent in the “standard care” group.<sup>30</sup> Our 2016 review also included a systematic review of six controlled clinical studies by Renner;<sup>31</sup> the authors concluded that the evidence “indicates that trained mid-level providers may effectively and safely provide first trimester surgical and medical termination of pregnancy services.” Additionally, Barnard et al., in a Cochrane systematic review, assessed the safety and effectiveness of abortion procedures administered by mid-level providers (nurse practitioners, midwives, other non-physician healthcare providers) compared to doctors.<sup>32</sup> The authors concluded, based in part on two of the studies that we had reviewed in 2016,<sup>33</sup> that there was no statistically significant difference in the risk of failure for medical abortions performed by mid-level providers compared with doctors.

We also believe that the identification of patients for whom the use of mifepristone is contraindicated can be done by mid-level healthcare providers, as well as physicians. Mifepristone in a regimen with misoprostol for medical termination of intrauterine pregnancy through 70 days gestation is contraindicated in patients with any of the following conditions:<sup>34</sup>

- Confirmed or suspected ectopic pregnancy or undiagnosed adnexal mass

<sup>26</sup> Olavarrieta CD, Ganatra B, Sorhaindo A, et al. Nurse versus Physician-provision of Early Medical Abortion in Mexico: A Randomized Controlled Non-Inferiority Trial. *Bull World Health Organ.* 2015;93:249-258.

<sup>27</sup> Kopp Kallner H, Gomperts R, Salomonsson E, et al. The efficacy, safety and acceptability of medical termination of pregnancy provided by standard care by doctors or by nurse-midwives: a randomised controlled equivalence trial. *BJOG.* 2015; 122: 510-517.

<sup>28</sup> Warriner IK, Wang D, et al. Can midlevel health-care providers administer early medical abortion as safely and effectively as doctors? A randomized controlled equivalence trial in Nepal. *Lancet.* 2011; 377: 1155-61.

<sup>29</sup> Puri M, Tamang A, Shrestha P, et al. The role of auxiliary nurse-midwives and community health volunteers in expanding access to medical abortion in rural Nepal. *Reproductive Health Matters.* 2015; 22(44) 94-103.

<sup>30</sup> 2016 Clinical Review, supra n. 13, at 43.

<sup>31</sup> Renner RM, Brahmi D, Kapp N. Who can provide effective and safe termination of pregnancy care? A systematic review. *BJOG* 2013 Jan;120(1):23-31.

<sup>32</sup> Barnard S, Kim C, Park MN, Ngo TD. Doctors or mid-level providers for abortion (Review). *Cochran Database of Systematic Reviews.* 2015, Issue 7.

<sup>33</sup> Of the medical abortion studies reviewed by Barnard et al (Id.), two were reviewed by the Agency as part of the review of the S-020 supplement in 2016. See Warriner et al (supra n. 28) and Kopp Kallner et al (supra n. 27). The third used a different dose of misoprostol than the currently approved regimen. See Jejeebhoy SJ, Kalyanwalaa S, Zaviera AJF, Kumara R, Mundleb S, Tankc J, et al. Feasibility of expanding the medication abortion provider based in India to include ayurvedic physicians and nurses. *International Perspectives on Sexual and Reproductive Health* 2012;38(3)133-42)

<sup>34</sup> See [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2019/020687s022lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020687s022lbl.pdf).



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- An intrauterine device in place
- Chronic adrenal failure
- Concurrent long-term corticosteroid therapy
- History of allergy to mifepristone, misoprostol, or other prostaglandins
- Hemorrhagic disorder or concurrent anticoagulant therapy
- Inherited porphyrias

These contraindications can be assessed by trained healthcare providers who prescribe mifepristone by obtaining a medical history, from medical records, and/or from physical examination or ultrasound if appropriate. We continue to believe that available data support the conclusion that mid-level healthcare providers, as well as physicians, possess the clinical and counseling skills necessary to provide medical abortion. We note this is consistent with ACOG's statement in its current practice bulletin that "[i]n addition to physicians, advanced practice clinicians, such as nurse-midwives, physician assistants, and nurse practitioners, possess the clinical and counseling skills necessary to provide first-trimester medical abortion."<sup>35</sup> Further, if necessary, ultrasound training and certification is available to nurse practitioners and physician assistants, as well as physicians.<sup>36</sup> In sum, available information supports that mid-level healthcare providers as well as physicians can determine whether mifepristone is an appropriate treatment for a particular patient and dispense it.

You also assert that FDA should strengthen the requirement that providers accurately assess the duration of the pregnancy by mandating that gestational age be assessed by ultrasound (Petition at 5). We refer you to FDA's 2016 Response to the citizen petition submitted to Docket No. FDA-2002-P-0364 (the "2016 CP Response"), where FDA stated that the determination of gestational age does not always require an ultrasound. In the 2016 CP Response, FDA stated it had "determined that it was inappropriate for us to mandate how providers clinically assess women for duration of pregnancy and for ectopic pregnancy. These decisions should be left to the professional judgment of each provider, as no method (including TVS [transvaginal ultrasound]) provides complete accuracy. The approved labeling for Mifeprex recommended ultrasound evaluation as needed, leaving this decision to the judgment of the provider."<sup>37</sup>

In the Petition, you reference the Prescriber Agreement Form, in which the provider must attest they have the ability to: (1) accurately assess the duration of the pregnancy; (2) diagnose ectopic pregnancies; and (3) provide surgical intervention if needed (or have made plans to provide such care through others), and you state that a provider who does not physically meet with and examine a patient, but simply consults with the patient over the Internet, is not capable of fulfilling these requirements, or of ruling out additional

<sup>35</sup> ACOG Practice Bulletin No. 225, *supra* n. 22.

<sup>36</sup> American Institute of Ultrasound in Medicine. Accessed November 26, 2021. <https://www.aium.org/officialStatements/70>.

<sup>37</sup> FDA's citizen petition response dated March 29, 2016, to the citizen petition submitted by the American Association of Pro-Life Obstetricians and Gynecologists, the Christian Medical and Dental Association, and Concerned Women for America on August 20, 2002, Docket No. FDA-2002-P-0364 at 18. See <https://www.regulations.gov/document/FDA-2002-P-0364-0002>.



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contraindications (Petition at 5-6). You state that FDA should require certified prescribers to be physically present when Mifeprex is dispensed so that they can appropriately examine patients and rule out contraindications to the use of Mifeprex (Petition at 4).

Certified prescribers do not have to be physically present with the patient as long as they have confirmed the patient's gestational age and intrauterine pregnancy. As noted above, in the 2016 CP response, FDA "determined that it was inappropriate for us to mandate how providers clinically assess women for duration of pregnancy and for ectopic pregnancy."<sup>38</sup> Moreover, the evaluation of patients for contraindications to medical abortion does not necessarily require direct physical contact with the certified prescriber and can be done in different types of healthcare settings. A certified prescriber can also review the Patient Agreement Form<sup>39</sup> with the patient, fully explain the risks of the mifepristone treatment regimen, and answer any questions, as in any consent process, without physical proximity. See also section II.B.1.c (ETASU C – In-person Dispensing).

With respect to providing surgical intervention in cases of incomplete abortion or severe bleeding and assuring patient access to medical facilities equipped to provide blood transfusions and resuscitation (if necessary), the Prescriber Agreement Form does not reflect a requirement that the certified prescriber must provide such care personally; rather, the prescriber must agree that they have the ability to provide such care or that they have made plans to provide such care through others, and that they have the ability to assure the patient has access to appropriate medical facilities. It is common practice for healthcare providers to provide emergency care coverage for other healthcare providers' patients, and in many places, hospitals employ "hospitalists" to provide care to all hospitalized patients. We also note ACOG's statement that "[i]n rare cases, a patient who undergoes a medication abortion may need to obtain an additional intervention, such as uterine aspiration. If the prescribing clinician does not perform the intervention, it is medically appropriate to provide a referral."<sup>40</sup>

For these reasons, we deny your request that FDA limit the "ability" to prescribe and dispense mifepristone to licensed physicians, and we deny your request that FDA require certified providers to physically meet with and examine the patient.

#### **b. Office Visits and Administration of Mifepristone/Misoprostol**

In the Petition, you state that the use of mifepristone and misoprostol should require three office visits by the patient (Petition at 7). In support of this position, you state the following:

- Drug-induced abortion is contraindicated for patients who are not available for follow-up contact or evaluation (Petition at 10).

<sup>38</sup> Id.

<sup>39</sup> See <https://www.accessdata.fda.gov/scripts/cder/remis/index.cfm?event=RemsDetails.page&REMS=390>.

<sup>40</sup> ACOG Practice Bulletin Number 225 supra n. 22.

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- Abortion complications are more frequent when women abort at home and more healthcare oversight is needed (Petition at 8).
- Home administration of misoprostol does not permit healthcare providers to control when their patients take misoprostol and without monitoring:
  - a patient may take buccal misoprostol before the minimum 24-hour period after taking Mifeprex, which leads to a significantly increased failure rate (Petition at 7).
  - a patient may swallow misoprostol rather than administer it buccally, and oral administration is not as effective as buccal administration in ending the pregnancy (Petition at 7).
- Because providers may now “confirm” that a patient’s drug-induced abortion was successful without a clinic visit, this increases the threat that Rh-negative patients will not receive Rhogam, which is necessary to prevent serious risks in subsequent pregnancies (Petition at 7 and 9).

We address each of these points below.

#### **i. Follow-up Care**

The safe use of mifepristone when used in the approved regimen with misoprostol is not contingent on a specific number of office visits being made by the patient undergoing a medical termination of pregnancy. The 2016 labeling change for Mifeprex regarding post-treatment assessment, including the change to the approved regimen to reduce the number of office visits from three to one, was based on evidence reviewed in the S-020 efficacy supplement. We concluded, upon reviewing the data, that three office visits were not necessary to assure the safe use of Mifeprex.<sup>41</sup>

In your Petition, you point to statements by ACOG that medical abortion is contraindicated for patients who are not available for follow-up contact or evaluation (Petition at 8, 10). The ACOG statements you point to are from ACOG Practice Bulletin No. 143, which has been withdrawn and replaced by Practice Bulletin No. 225.<sup>42</sup> Neither of the statements from the withdrawn Practice Bulletin nor Practice Bulletin No. 225 contraindicate medical abortion in women who are not available for an in-clinic follow-up visit. The current ACOG recommendations indicate that for medical abortion, “[f]ollow-up can be performed by telephone at 1 week, with subsequent at-home urine pregnancy testing at 4 weeks after treatment, which avoids the need for the patient to go to a facility.”<sup>43</sup> The patient and their healthcare provider should determine the best option for follow-up as part of the consultation and consent process.<sup>44</sup> As reflected in ACOG’s guidance, appropriate follow-

<sup>41</sup> See 2016 Clinical Review, supra n. 13, at 44 and 64-67.

<sup>42</sup> ACOG Practice Bulletin Number 225, supra n. 22.

<sup>43</sup> Id.

<sup>44</sup> Id.

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up after medical termination of a pregnancy may be accomplished in multiple ways and not all require an in-clinic visit.

You also question findings in multiple studies that evaluated the effectiveness of semiquantitative urine pregnancy tests (multi-level pregnancy tests, or MLPT) and low sensitivity urine pregnancy tests (LSPT) to rule out on-going pregnancies and assessed the ability of patients to self-administer these tests and interpret the test results (Petition at 9-10). Overall, these studies concluded that in the majority of women, it is feasible to use a simplified test to determine if further follow-up is necessary. A recent systematic review and meta-analysis by Baiju assessed the effectiveness and safety of self-assessment of the outcome of medical abortion completed at home versus routine clinic follow-up after medical abortion, concluding self-assessment was not inferior to routine clinic follow-up.<sup>45</sup> We note that this is consistent with current ACOG recommendations, which state that “follow-up can be performed by telephone at 1 week, with subsequent at-home urine pregnancy testing at 4 weeks after treatment, which avoids the need for the patient to go to a facility.”<sup>46</sup>

You also assert that it is important for a patient to be under observation after taking misoprostol to ensure that they are appropriately monitored and provided sufficient pain medication (Petition at 8). You cite the World Health Organization (WHO)’s statement in guidance that up to 90 percent of women will abort within 4-6 hours after taking misoprostol; you further state that the 2000 regimen permitted patients to be in the clinic during this time period (Petition at 8). Your reference to the WHO guidance document<sup>47</sup> appears to be out of context. The WHO guidance takes no position on whether women should return to and remain in the clinic during a follow-up visit for purposes of taking misoprostol; in fact, it explicitly recognizes that post-abortion care may not require a follow-up visit if the patient is adequately counseled.<sup>48</sup> In the United States, and as reflected in the approved labeling, medical termination of pregnancy usually involves patients terminating the pregnancy at home, with appropriate follow-up that may not include a return visit.

## ii. At Home Medical Abortion and Healthcare Oversight

In addition, you cite a 2018 study to support your statement that abortion complications are more frequent when women abort at home (Petition at 8). The study evaluated complications following medical abortion (both less than 12 weeks and more than 12 weeks gestation) as well as following surgical abortion, at one hospital in Sweden between 2008 and 2015.<sup>49</sup> For the years 2008 to 2010, data were collected retrospectively; for the years

<sup>45</sup> Baiju, N, Acharya, G, D’Antonio, F, et al. 2019. Effectiveness, safety and acceptability of self-assessment of the outcome of first-trimester medical abortion: a systematic review and meta-analysis. BJOG; 126:1536-1544.

<sup>46</sup> ACOG Practice Bulletin Number 225, supra n. 22.

<sup>47</sup> World Health Organization, Safe Abortion: technical and policy guidance for health systems – 2<sup>nd</sup> edition. 2012. Page 45 and Section 2.2.2.1 Medication for pain.

<sup>48</sup> Id. at Section 2.3 Post-abortion care and follow-up, at 52.

<sup>49</sup> Carlsson I, Breeding K, Larsson PG, 2018, Complications Related to Induced Abortion: A Combined Retrospective and Longitudinal Follow-up Study, BMC Women’s Health 18:158.

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2011 to 2015, data were collected prospectively. In this study, medical abortions after 12 gestational weeks all occurred at the hospital. The authors report that, among medical abortions less than 12 weeks, the complication frequency increased from 5.4 percent (2008 to 2010) to 8.2 percent (2015). However, the authors also compared the complications related to medical abortions that occurred at less than 12 gestational weeks between “at home” abortions (managed as an outpatient) and “at the hospital” abortions, in 2015 and found no statistically significant difference (8.2 percent “at home” versus 8.0 percent at the hospital). For pregnancies less than or equal to 9 gestational weeks, the rates are similar for the “at home” group (10.0 percent) and the “at the hospital” group (9.3 percent). Notably, as part of our review and approval of the S-020 efficacy supplement in 2016, we assessed serious adverse events by gestational age, including hospitalizations, serious infection requiring hospitalization or intravenous antibiotics, bleeding requiring transfusion, and ectopic pregnancy, as reported in the literature submitted by the Applicant. We concluded that these serious adverse events are rarely reported in the literature and that the regimen of mifepristone 200 mg followed by buccal misoprostol 800 mcg in 24-48 hours is safe to approve for use through 70 days gestation.<sup>50</sup>

You also state that medical abortion is a longer process than surgical abortion and that it requires more attention and care from healthcare providers (Petition at 10). We agree that medical abortion can be a longer process than surgical abortion,<sup>51</sup> but we disagree that medical abortion always requires in-person follow-up with a healthcare provider. Not all of the complications associated with medical abortion necessarily require more intensive management from healthcare providers during a follow-up visit. The question of whether to include an in-person follow-up visit should be discussed by the healthcare provider and the patient. We have concluded that medical abortions are safe and effective for patients who are appropriate candidates and reducing the number of clinic visits does not compromise patient safety.

The current approved labeling for mifepristone for medical termination of pregnancy states that complete pregnancy termination “can be confirmed by medical history, clinical examination, human Chorionic Gonadotropin (hCG) testing, or ultrasonographic scan.” Not all these modalities require an in-clinic assessment during a follow-up visit. Our review of the S-020 efficacy supplement concluded that “available data support ... that there are a variety of follow-up modalities that can adequately identify the need for additional intervention.”<sup>52</sup> We note that these findings are also consistent with ACOG guidelines, which state that “[r]outine in-person follow-up is not necessary after uncomplicated medication abortion” and recommend several methods for post-treatment follow-up, as appropriate, including serial serum hCG testing alone or telephone follow-up at one week after treatment followed by urine pregnancy testing at four weeks after treatment.<sup>53</sup> Because there is more than one effective method to detect an on-going pregnancy, we conclude that the way in which post-treatment follow-up is performed may be determined by the healthcare provider and the patient.

<sup>50</sup> 2016 Clinical Review, supra n. 13, at 51-57.

<sup>51</sup> See ACOG Practice Bulletin Number 225, supra note 22.

<sup>52</sup> 2016 Cross Discipline Team Leader Review, supra n. 19, at 17.

<sup>53</sup> ACOG Practice Bulletin Number 225, supra note 22.

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### iii. Misoprostol

In the Petition, you make a number of assertions regarding the use of misoprostol. We address each in turn.

First, you assert that a patient may take misoprostol before the prescribed minimum 24-hour period after taking Mifeprex, thereby rendering the regimen ineffective, and that home administration of misoprostol does not permit health providers to control when their patients take misoprostol (Petition at 7). You similarly assert that the use of buccal misoprostol sooner than 24 hours after administering mifepristone leads to significantly increased failure rates (Petition at 7).

As an initial matter, our review of the S-020 efficacy supplement in 2016 included data that evaluated the home use of misoprostol in over 30,000 women. The data showed that Mifeprex was safe and effective in a regimen with misoprostol when misoprostol was self-administered at home.<sup>54</sup> Therefore, any incorrect administration resulting in a failed abortion was infrequent and did not significantly affect the safety and efficacy of medical abortion. Furthermore, because the process of expelling the pregnancy may begin as soon as 2 hours after taking misoprostol, there is a benefit in allowing patients to choose when and where to start this process, to maximize the possibility of their being at a safe place at a convenient time to experience cramping and bleeding.<sup>55</sup>

In support of your assertion of significantly increased failure rates, you cite a pilot study by Lohr et al.<sup>56</sup> Lohr et al. assessed the complete abortion rate using simultaneous oral mifepristone and buccal misoprostol in three gestational age groupings (less than or equal to 49 days, 50-56 days, 57-63 days) and compared the rates with those published in previous pilot investigations<sup>57</sup> using simultaneous oral mifepristone and vaginal misoprostol in the same three gestational age groupings. The complete abortion rates reported by Lohr at 24 hours for oral mifepristone and buccal misoprostol were 72.5 percent, 69.2 percent, and 72.5 percent, respectively; the complete abortion rates at two weeks, however, were 97.5 percent, 100 percent, and 94.9 percent, respectively (and are consistent with the completion rates as described in the approved labeling).<sup>58</sup> The published complete abortion rates at 24 hours for simultaneous oral mifepristone and vaginal misoprostol administration were 90 percent, 88 percent, and 83 percent, respectively, for the gestational age groupings and the complete abortion rates at 2 weeks were 98 percent, 93 percent, 90 percent, respectively. Based on the data presented in Lohr,

<sup>54</sup> See 2016 Clinical Review, *supra* n. 13, at 41 and 48.

<sup>55</sup> *Id.* at 38.

<sup>56</sup> Petition at 7 (referencing Lohr PA, Reeves MF, Hayes JL, et al., 2007, Oral Mifepristone and Buccal Misoprostol Administered Simultaneously for Abortion: A Pilot Study, *Contraception*, 76:215-220).

<sup>57</sup> Schreiber CA, Creinin MD, Harwood B, Murthy AS. A pilot study of mifepristone and misoprostol administered at the same time for abortion in women with gestation from 50 to 63 days. *Contraception* 2005;71:447-50; Murthy AS, Creinin MD, Harwood B, Schreiber C. A pilot study of mifepristone and misoprostol administered at the same time for abortion up to 49 days gestation. *Contraception* 2005;71:333-6.

<sup>58</sup> See [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2019/020687s022lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020687s022lbl.pdf).



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the use of buccal misoprostol at the same time as oral mifepristone does not adversely affect efficacy, although expulsion may be delayed. As recommended in Section 2.3 of the approved labeling, follow-up at 7-14 days after administration of mifepristone is more appropriate to evaluate efficacy.<sup>59</sup> It is misleading to only reference the abortion completion rates observed at the 24-hour timepoint from Lohr. Therefore, we do not agree that data from Lohr indicate higher failure rate with misoprostol taken before the prescribed minimum 24-hour period after taking mifepristone.

Although we disagree that Lohr demonstrates a higher failure rate with misoprostol taken before 24-hours after taking mifepristone, we note that our 2016 review of the S-020 efficacy supplement referenced a 2013 systematic review by Raymond, which concluded that if the interval between mifepristone and misoprostol interval is less than or equal to 24 hours, the procedure is less effective compared to an interval of 24-48 hours.<sup>60</sup> As explained above, the data reviewed in 2016 showed that Mifeprex, in a regimen with misoprostol administered at home, was safe and effective. Therefore, incorrect administration, if it occurred, was infrequent and did not significantly affect the safety and efficacy of medical abortion. However, in light of the data reviewed, section 2.1 of the labeling approved in 2016 (as well as the currently approved labeling and Medication Guide) states that there should be a “minimum 24-hour interval between” mifepristone and misoprostol (emphasis included in the labeling).<sup>61</sup> The approved dosing regimen also states that misoprostol is taken within 24 to 48 hours after taking mifepristone and acknowledges that the effectiveness of the regimen may be lower if misoprostol is administered less than 24 hours after mifepristone administration.

In addition to your concerns that a woman may take misoprostol too soon after administering mifepristone, you also state that waiting until 24 hours after administering mifepristone does not guarantee success (Petition at 7-8). In support of this concern, you cite a 2015 review by Chen and Creinin. You state that this review found “women taking misoprostol earlier than 48 hours after Mifeprex are more likely to fail the regimen” (Petition at 8). Chen and Creinin included studies in which the intervals between mifepristone and buccal misoprostol were 24 hours or 24-48 hours and stated that “based on the available literature, the overall efficacy of regimens with a 24-hour interval between mifepristone and buccal misoprostol is significantly lower than those with a 24- to 48-hour interval (94.2 percent compared with 96.8 percent).”<sup>62</sup> The rate differences were statistically significant, but both regimens were more effective than the 92 percent efficacy rate of the original regimen approved in 2000 (administering misoprostol 48 hours after taking mifepristone).

Finally, you also express concern that if misoprostol is self-administered, a woman may swallow it rather than keep the pill between her cheek and gum, and oral administration of

<sup>59</sup> See [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2019/020687s022lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020687s022lbl.pdf).

<sup>60</sup> 2016 Clinical Review, supra n. 13, at 31 (citing 8 Raymond EG, et al. First-trimester medical abortion with mifepristone 200 mg and misoprostol: a systematic review. *Contraception* 2013;87(1):26-37.)

<sup>61</sup> See [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2019/020687s022lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020687s022lbl.pdf).

<sup>62</sup> See Chen MJ and Creinin MD. Mifepristone with buccal misoprostol for medical abortion. *Obstet Gynecol.* 2015;126(1):12-21; see also 2016 Clinical Review, supra n. 13, at 21.



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misoprostol (i.e., swallowing the pill) following the lower dose of mifepristone in the current regimen is not as effective in ending the pregnancy (Petition at 7). Winikoff et al. specifically studied the use of oral compared to buccal misoprostol 24-36 hours after mifepristone 200 mg with overall success rates of 91.3 percent and 96.2 percent, respectively.<sup>63</sup> Both regimens resulted in a greater than 91 percent successful medical abortion. Although the study showed decreased efficacy with oral versus buccal administration in 57-63 days gestational age, there were no statistical differences in other gestational age groupings. Even assuming there is a small proportion of women who are 57-63 days gestational age and use oral administration of misoprostol (rather than buccal as labeled), a small decrease in the reported efficacy in that population would not justify requiring a clinic visit for all women undergoing medical abortion.

Overall, studies support the efficacy of the mifepristone, in a regimen with misoprostol when taken by the patient at home. Therefore, we do not agree that an in-person visit is necessary to manage administration of misoprostol.

### iii. Rh-Negative Patients

In the Petition, you state that a follow-up examination is particularly critical for Rh-negative patients and that without that follow-up examination, women will not receive Rhogam after the abortion, increasing their risk of subsequent Rh isoimmunization, which can endanger future pregnancies (Petition at 9). You suggest that a clinic visit after the administration of Mifeprex is important for Rh-negative women to receive Rhogam and that removing the required follow-up visit puts Rh-negative women at risk for isoimmunization. We do not agree.

Rh testing is standard of care in the United States and RhD immunoglobulin (such as Rhogam) should be administered if indicated. Further, administration of RhD immunoglobulin should be given within 72 hours of a sensitizing event (e.g., medical abortion).<sup>64</sup> However, the facility where the RhD immunoglobulin injection occurs (clinic, hospital or laboratory) is not critical. A shift from medical clinics to hospitals for administration of injections has occurred over the years due to shortages of RhD immunoglobulin and poor reimbursement for RhD immunoglobulin injection from third-party payers.<sup>65</sup> This has resulted in pregnant women frequently obtaining routine 28-week RhD immunoglobulin injections at hospitals/laboratories with a prescription provided by their healthcare providers. This same process of obtaining RhD immunoglobulin via prescription is available to patients after medical termination of pregnancy and does not require a follow-up clinic visit.

<sup>63</sup> Winikoff B, Dzuba, IG, Creinin MD, et al, 2008, Two Distinct Oral Routes of Misoprostol in Mifepristone Medical Abortion, *Obstet Gynecol* 112(6):1303-1310.

<sup>64</sup> ACOG Practice Bulletin No. 181. Prevention of Rh D Alloimmunization. August 2017.

<sup>65</sup> See <https://www.mdedge.com/obgyn/article/61083/practice-management/rhogam-injections-payment-levels-vary-among-insurers>.

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In summary, the totality of data on the efficacy and safety of medical abortion at less than 70 days gestation, derived from numerous studies, has characterized the complications and rates of complications for completing medical abortion at home, and the findings show medical abortion at home is both safe and effective without three office visits. We therefore deny your request that the use of mifepristone in a regimen with misoprostol require three office visits by the patient.

### c. Contraindications

In the Petition, you assert that critical language contraindicating Mifeprex for patients without access to appropriate emergency medical care was excluded from the 2016 Mifeprex labeling. You cite to a study<sup>66</sup> and ACOG statements as evidence that medical abortions have greater risks and more need for emergency “operation” than a surgical abortion, particularly for patients in rural areas with limited access to emergency medical care (Petition at 11).

Although inadequate access to medical facilities for appropriate care was removed from the list of contraindications in section 4 of the approved labeling when we approved the S-020 efficacy supplement, the 2016 Mifeprex labeling and the currently approved mifepristone labeling, as well as the Mifepristone REMS Program, continue to include appropriate instructions for providers regarding patient access to appropriate medical care.<sup>67</sup> For example, the Boxed Warning includes language directing healthcare providers to ensure that the patient knows whom to call and what to do, including potentially going to an emergency room, if the patient experiences serious events associated with the use of mifepristone. The labeling also directs healthcare providers, as part of the dosing regimen, to give the patient the name and phone number of a healthcare provider who will be handling emergencies.<sup>68</sup> In addition, one of the required qualifications listed in the Prescriber Agreement Form is the “[a]bility to provide surgical intervention in cases of incomplete abortion or severe bleeding, or to have made plans to provide such care through others, and ability to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.”<sup>69</sup> Therefore, although certain language about access to medical facilities was removed from the approved labeling in 2016, we disagree that critical language about access to appropriate emergency medical care is lacking from the approved labeling.

<sup>66</sup> See Petition Reference Document No. 17 (Harrison Affidavit: Donna Harrison, M.D., Aff. *Okla. Coalition for Reproductive Justice v. Cline*, Case No. CV-2014-1886 (Feb. 24, 2015), ¶115 (referencing M. Niinimäki et al., Immediate Complications after Medical compared with Surgical Termination of Pregnancy, *Obstet. Gynecol.* 114:795 (Oct. 2009)).

<sup>67</sup> See Mifeprex labeling, approved 2016.

[https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2016/020687s020lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020687s020lbl.pdf). See also current labeling at [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2019/020687s022lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020687s022lbl.pdf).

<sup>68</sup> Id.

<sup>69</sup> Mifepristone REMS Program,

<https://www.accessdata.fda.gov/scripts/cder/remis/index.cfm?event=RemsDetails.page&REMS=390>.

Emphasis added.

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You also cite information in Box 1, Features of Medical and Surgical Abortion (page 3) in the ACOG Practice Bulletin No. 143.<sup>70</sup> As mentioned above, the ACOG Practice Bulletin No. 143 has been withdrawn and the language you cite is not included in the current Practice Bulletin No. 225.

#### **d. Adverse Event Reporting**

In the Petition, you assert that even under the regimen approved in 2000, it was difficult to collect accurate and complete adverse event information for Mifeprex, and that collecting such information is virtually impossible under the regimen approved in 2016 because prescribers only are required to report deaths associated with Mifeprex (Petition at 12). You also assert that FDA cannot adequately assess the safety of the current Mifeprex regimen without comprehensive information on adverse events (Petition at 12). You state that certified prescribers should at a minimum be required to report the following to FDA's MedWatch reporting system and to the sponsor: deaths, hospitalizations, blood transfusions, emergency room visits, failures requiring surgical completion, ongoing pregnancy, or other major complications, including detailed information on these events (Petition at 13).

We acknowledge that there is always a possibility with any drug that some adverse events are not being reported, because reporting to the Agency's MedWatch program by health care professionals and patients is voluntary. We do not agree, however, that the 2016 changes to the prescriber reporting requirements limit our ability to adequately monitor the safety of mifepristone for medical termination of pregnancy. Prior to the 2016 approval of the S-20 efficacy supplement, we assessed approximately 15 years of adverse event reports both from the Applicant and through the MedWatch program and determined that certain ongoing additional reporting requirements under the Mifeprex REMS, such as hospitalization and blood transfusions, were not warranted. This assessment was based on the well-characterized safety profile of Mifeprex, with known risks occurring rarely, along with the essentially unchanged safety profile of Mifeprex during this 15-year period of surveillance. Accordingly, the Prescriber Agreement Form was amended as part of our 2016 approval of the S-20 efficacy supplement to require, with respect to adverse event reporting, only that prescribers report any cases of death to the Applicant.

We also note that the reporting changes to the Prescriber Agreement Form as part of our 2016 approval do not change the adverse event reporting requirements for the Applicants. Like all other holders of approved NDAs and ANDAs, the Applicants are required to report all adverse events, including serious adverse events, to FDA in accordance with the requirements set forth in FDA's regulations (see 21 CFR 314.98, 21 CFR 314.80, and 21 CFR 314.81). FDA also routinely reviews the safety information provided by the Applicants in the Annual Reports. As with all drugs, FDA continues to closely monitor the postmarketing safety data on mifepristone for the medical termination of pregnancy.

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<sup>70</sup> Petition at 11. Medical Management of First-Trimester Abortion. ACOG Practice Bulletin Number 143. March 2014 (Reaffirmed 2016. Replaces Practice Bulletin Number 67, October 2005); Obstet Gynecol. 2014 Mar;123(3):676-692 at 680.

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You state that FDA should provide guidance to emergency healthcare providers and physicians so that they know how to distinguish complications following drug-induced abortion from complications following spontaneous miscarriage (Petition at 13). We disagree that specific guidance is needed at this time. In the past, when appropriate, FDA has worked with the NDA Applicant to issue communications to healthcare providers and emergency department providers concerning certain serious adverse events.<sup>71</sup> Furthermore, the approved Medication Guide advises patients to take the Medication Guide with them if they need to go to the emergency room or seek care from a healthcare provider other than the one who dispensed the medication to them, so the emergency room or healthcare provider understands the patient is having a medical abortion. We have not identified a change in the safety profile of mifepristone that would warrant additional communications to healthcare providers and emergency department providers concerning complications following medical abortion. If we become aware of safety information that merits further communications with emergency department providers or healthcare providers, or that warrants revisions to the approved labeling, we will act as appropriate.

You also assert that many Mifeprex prescribers “violate FDA protocol,” instructing their patients to lie to emergency medical personnel, and that this prevents emergency healthcare providers from appropriately caring for their patients and further decreases the likelihood that adverse events will be reported (Petition at 12). Your only support for this claim is a reference to instructions from the organization Aid Access<sup>72</sup> to patients that they can tell emergency room staff that they had a miscarriage and do not need to tell medical staff that they had a medical abortion. The Petition does not provide any data or additional information establishing “many Mifeprex prescribers violate FDA protocol, instructing their patients to lie,” or that these providers thereby prevented appropriate care and decreased the number of adverse events reported.

## **B. REMS**

### **1. Request to Retain Mifeprex REMS**

In your Petition, you request that FDA retain the Mifeprex REMS (Petition at 14). We agree that a REMS is necessary to ensure that the benefits of mifepristone in a regimen with misoprostol outweigh the risks. FDA’s determination as to whether a REMS is necessary

<sup>71</sup> See Historical Information on Mifepristone (Marketed as Mifeprex), available at <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111334.htm>. For example, the NDA applicant and FDA agreed that there was a need to issue a Dear Health Care Provider letter in April 2002 and a Dear Emergency Room Director letter in September 2004. The fact that these letters were issued does not imply that the approved mifepristone regimen is unsafe; it is not uncommon for drug sponsors to issue “Dear Health Care Provider” letters, and, as noted in the Mifepristone Q&A document posted on our Web site in April 2002, “[w]hen FDA receives and reviews new information, the agency provides appropriate updates to doctors and their patients so that they have essential information on how to use a drug safely.”

<sup>72</sup> We note that Aid Access facilitated the sale of unapproved mifepristone and misoprostol to U.S. consumers and that FDA sent Aid Access a warning letter asking it to promptly cease causing the sale of unapproved and misbranded drugs to U.S. consumers. US FDA Warning Letter to Aidaccess.org, dated March 8, 2019. <https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/aidaccessorg-575658-03082019>.

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to ensure that the benefits of a drug outweigh its risks is a complex, drug-specific inquiry, reflecting an analysis of multiple, interrelated factors and of how those factors apply in a particular case.<sup>73</sup> In conducting this analysis, FDA considers whether (based on premarketing or postmarketing risk assessments) there is a particular risk or risks associated with the use of the drug that, on balance, outweigh its benefits and whether additional interventions beyond FDA-approved labeling are necessary to ensure that the drug's benefits outweigh its risks.<sup>74</sup>

As described in the background section of this response (see section I.A.), FDA determined that interventions in addition to the FDA-approved labeling were necessary to ensure that the benefits of Mifeprex outweighed its risks when the drug was initially approved in 2000, and periodic re-evaluations of the REMS since that time have reached the same conclusion. As further described in the background section of this response (see section I.E.), FDA recently undertook a review of the Mifepristone REMS Program. As explained below, the Mifepristone REMS Program continues to be necessary to ensure the benefits outweigh the risks.

After review of multiple different sources of information, including published literature, safety information submitted to the Agency during the COVID-19 PHE, FAERS reports, the first REMS assessment report for the Mifepristone REMS Program, and information provided by advocacy groups, individuals, and the Plaintiffs in ongoing litigation,<sup>75</sup> as well as information submitted by the Applicants, we have concluded that the REMS can be modified to reduce the burden on the health care delivery system without compromising patient safety. As explained below, we agree that the healthcare provider certification (ETASU A) and dispensing of mifepristone to patients with evidence or other documentation of safe use conditions (ETASU D) continue to be necessary components of the REMS to ensure the benefits outweigh the risks. However, we have concluded that the Mifepristone REMS Program must be modified to remove the requirement under ETASU C that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals.

Below, we discuss each of these elements of the Mifepristone REMS Program.

#### **a. ETASU A – Prescriber Certification/Qualifications**

ETASU A under the Mifepristone REMS Program requires healthcare providers who prescribe mifepristone to be certified. In order to become certified, prescribers must: 1) review the prescribing information for mifepristone and 2) complete the Prescriber Agreement Form. In signing the Prescriber Agreement Form, prescribers agree they meet the qualifications listed below:

<sup>73</sup> See FDA Guidance for Industry, *REMS: FDA's Application of Statutory Factors in Determining When a REMS Is Necessary* (Apr. 2019).

<sup>74</sup> *Id.*

<sup>75</sup> See *supra* n. 10.



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- Ability to assess the duration of pregnancy accurately
- Ability to diagnose ectopic pregnancies
- Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or to have made plans to provide such care through others, and ability to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.
- Has read and understood the Prescribing Information of mifepristone (which the provider can access by phone or online).

In addition to meeting these qualifications, as a condition of certification the healthcare provider also agrees to follow the guidelines for use below:

- Review the Patient Agreement Form with the patient and fully explain the risks of the mifepristone treatment regimen. Answer any questions the patient may have prior to receiving mifepristone.
- Sign and obtain the patient's signature on the Patient Agreement Form.
- Provide the patient with a copy of the Patient Agreement Form and the Medication Guide.
- Place the signed Patient Agreement Form in the patient's medical record.
- Record the serial number from each package of mifepristone in each patient's record.
- Report deaths to the Applicant, identifying the patient by a non-identifiable patient reference and the serial number from each package of mifepristone.

Our review of the published literature did not identify any studies comparing healthcare providers who met these qualifications with healthcare providers who did not. In the absence of such studies, there is no evidence to contradict our previous finding that prescribers' ability to accurately date pregnancies, diagnose ectopic pregnancies, and provide surgical intervention either personally or through others, is necessary to mitigate the serious risks associated with the use of mifepristone in a regimen with misoprostol. Therefore, our conclusion continues to be that a healthcare provider who prescribes mifepristone in a regimen with misoprostol should meet the above qualifications. Absent these provider qualifications, we are concerned that serious and potentially fatal complications associated with medical abortion, including missed ectopic pregnancy and heavy bleeding from incomplete abortion, may not be detected or appropriately managed.

Accordingly, we have determined that ETASU A must remain an element of the Mifepristone REMS Program to ensure the benefits outweigh the risks. Maintaining the requirement for prescriber certification ensures that providers meet the necessary qualifications and adhere to the guidelines for use listed above. The burden of prescriber certification has been minimized to the extent possible by requiring prescribers to certify only one-time for each applicant.



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Although we agree with your request to retain the REMS for mifepristone (now the Mifepristone REMS Program) insofar as it pertains to ETASU A, as discussed in section II.A.2.a of this response, we do not agree with your request that the healthcare provider needs to be a licensed physician to meet this requirement.

**b. ETASU D – Requirement For The Drug To Be Dispensed With Evidence Or Other Documentation Of Safe-Use Conditions**

ETASU D under the Mifepristone REMS Program requires mifepristone to be dispensed with evidence or other documentation of safe-use conditions. To receive mifepristone for medical termination of intrauterine pregnancy through 70 days gestation, the patient must sign a Patient Agreement Form indicating that the patient has received, read, and been provided a copy of the Patient Agreement Form and received counseling from the prescriber regarding the risk of serious complications associated with mifepristone for this indication. The Patient Agreement Form ensures that patients are informed of the risks of serious complications associated with mifepristone for this indication. In a number of approved REMS, Patient Agreement Forms or Patient Enrollment Forms ensure that patients are counseled about the risks of the product and/or informed of appropriate safe use conditions.<sup>76</sup>

As a condition of certification under the Mifepristone REMS Program, healthcare providers must follow the guidelines for use of mifepristone, including reviewing the Patient Agreement Form with the patient, fully explaining the risks of the treatment regimen and answering any questions the patient may have before receiving the medication. With this form, the patient acknowledges that they have received and read the form, and that they have received the counseling regarding when to take mifepristone, the risk of serious complications associated with mifepristone and what to do if they experience adverse events (e.g., fever, heavy bleeding). Both the healthcare provider and patient must sign the document and the patient must receive a copy of the signed form. In addition to the counseling described in the Patient Agreement Form, patients also receive a copy of the Medication Guide for mifepristone. Ultimately, the Patient Agreement Form serves as an important counseling component, and documentation that the safe use conditions of the Mifepristone REMS Program have been satisfied, as the prescriber is required to place the signed Patient Agreement Form in the patient's medical record.

In addition, we conducted an updated review of published literature since 2016 to assess the utility of maintaining the Patient Agreement Form as part of the Mifepristone REMS Program, and these studies do not provide evidence that would support removing ETASU D. For these reasons, we have determined that ETASU D must remain an element of the Mifepristone REMS Program to ensure the benefits outweigh the risks.

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<sup>76</sup> REMS@FDA, <https://www.accessdata.fda.gov/scripts/cder/remis/index.cfm>, Accessed November 15, 2021.

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### c. ETASU C – In-Person Dispensing

ETASU C under the Mifepristone REMS Program currently requires mifepristone to be dispensed to patients only in certain healthcare settings, specifically clinics, medical offices, and hospitals, by or under the supervision of a certified prescriber. This creates what we refer to in this response as an in-person dispensing requirement under the REMS; i.e., the patient must be present in person in the clinic, medical office, or hospital when the drug is dispensed. The mifepristone REMS document currently states that mifepristone may not be distributed to or dispensed through retail pharmacies or settings other than a clinic, medical office, or hospital. As explained below, based on a recent review of the REMS, we believe that the Mifepristone REMS Program must be modified to remove the requirement that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals, because this requirement is no longer necessary to ensure that the benefits of the drug outweigh the risks. This conclusion is based on our review of information from the Mifepristone REMS Program one-year (1<sup>st</sup>) REMS<sup>77</sup> assessment data and postmarketing safety information, and supported by our review of the published literature.

#### i. Assessment Data

As part of our review of the REMS, we evaluated information included in the 1<sup>st</sup> REMS assessment report for the Mifepristone REMS Program, which included healthcare provider certification data, program utilization data, and non-compliance data. This 1<sup>st</sup> REMS assessment report covers a reporting period between April 11, 2019 through February 29, 2020. During this reporting period, a small number of non-compliance events were reported.

As described in section I.C. of this response, during the timeframe from January 27, 2020 through September 30, 2021, there were periods when the in-person dispensing requirement was not enforced. To better understand whether there was any impact on safety or non-compliance during the periods when the in-person dispensing requirement was not enforced, we requested additional information from the Applicants to provide for more comprehensive assessment of the REMS for the time period from January 27, 2020 (the effective date of the COVID-19 PHE) to September 30, 2021. We requested the Applicants provide a summary and analysis of any program deviation or non-compliance events from the REMS requirements and any adverse events that occurred during this time period that had not already been submitted to FDA. The NDA and the ANDA Applicants reported a total of eight cases reporting adverse events between January 27, 2020 and September 30, 2021. These eight cases were also identified in the FAERS database and are described below.

The number of adverse events reported to FDA during the COVID-19 PHE with mifepristone use for medical termination of pregnancy is small, and the data provide no

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<sup>77</sup> This REMS assessment report was the first submitted following the approval of the single, shared system REMS for mifepristone.

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indication that any program deviation or noncompliance with the Mifepristone REMS Program contributed to these reported adverse events.

## ii. FAERS/Postmarketing Safety Data

FDA routinely monitors postmarketing safety data for approved drugs through adverse events reported to our FAERS database,<sup>78</sup> through our review of published medical literature, and when appropriate, by requesting applicants submit summarized postmarketing data. For our recent review of the REMS, we searched our FAERS database, reviewed the published medical literature for postmarketing adverse event reports for mifepristone for medical termination of pregnancy, and requested that the Applicants submit a summary and analysis of certain adverse events. Our review of this postmarketing data indicates there have not been any new safety concerns with the use of mifepristone for medical termination of pregnancy through 70 days gestation, including during the time when in-person dispensing was not enforced.

In order to evaluate the periods when in-person dispensing was and was not enforced, we conducted a search of the FAERS database and the published medical literature to identify U.S. postmarketing adverse events that reportedly occurred from January 27, 2020 through September 30, 2021 with mifepristone use for medical termination of pregnancy. The data for this time period were then further divided into the date ranges when in-person dispensing was enforced per the REMS (January 27, 2020 - July 12, 2020 and January 13, 2021 - April 12, 2021) versus when in-person dispensing was not enforced: July 13, 2020 - January 12, 2021 (in-person dispensing enforcement was temporarily enjoined) and April 13, 2021 - September 30, 2021 (enforcement discretion for in-person dispensing because of the COVID-19 PHE).

Based on the above search, a total of eight cases were identified in FAERS and no additional case reports were identified in the medical literature. Two of the eight cases reported adverse events that occurred when in-person dispensing was being enforced (i.e., January 27, 2020-July 12, 2020 and January 13, 2021-April 12, 2021). These two cases reported the occurrence of uterine/vaginal bleeding (case 1) and uterine/vaginal bleeding and sepsis (case 2). Of note, uterine/vaginal bleeding and sepsis are labeled adverse events. Five of the eight cases reported adverse events that occurred when in-person dispensing was not enforced (i.e., July 13, 2020-January 12, 2021 and April 13, 2021-September 30, 2021); however, the narratives provided in the FAERS reports for three of the five cases explicitly stated that mifepristone was dispensed in-person. These five cases reported the occurrence of ongoing pregnancy (case 3), drug intoxication and death approximately 5 months after ingestion of mifepristone (case 4), death [cause of death is currently unknown] (case 5), sepsis and death (case 6), and pulmonary embolism (case 7). Of note, ongoing pregnancy and sepsis, including the possibility of fatal septic shock, are labeled adverse events. The remaining case reported the occurrence of oral pain/soreness (case 8) in July

<sup>78</sup> FAERS is a database that contains adverse event reports, medication error reports and product quality complaints resulting in adverse events that were submitted to FDA. The database is designed to support FDA's post-marketing safety surveillance program for drug and therapeutic biologic products.

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2021, but did not provide sufficient information to determine the exact date of the adverse event.

As discussed in section II.A.2.d., the Applicants report adverse events, including serious adverse events, to FDA in accordance with applicable regulations.<sup>79</sup> To enable additional review of adverse events, Applicants were requested to provide a summary and analysis for adverse events reported with incomplete medical abortion requiring surgical intervention to complete abortion, blood transfusion following heavy bleeding or hemorrhage, ectopic pregnancies, sepsis, infection without sepsis, hospitalization related to medical abortion, and emergency department/urgent care encounter related to medical abortion. The Applicant for Mifeprex provided the requested summary of postmarketing safety information from March 29, 2016, when S-020 was approved, through September 30, 2021. The Applicant for the generic provided the requested summary of postmarketing safety information from April 11, 2019 (date of initial approval) through September 30, 2021. The information provided by the Applicants included the same cases identified in FAERS, as discussed above.

We analyzed the FAERS data referenced above to determine if there was a difference in adverse events when in-person dispensing was and was not enforced. Based on FDA's review of this data, we concluded that there does not appear to be a difference in adverse events when in-person dispensing was and was not enforced and that mifepristone may be safely used without in-person dispensing. FDA's review of the summary and analysis data submitted by the Applicants (which, as noted above, included the same cases identified from FAERS) did not change this conclusion.

### iii. Published Literature

As noted above, we also conducted an extensive review of the published literature since March 29, 2016 (the date the S-020 efficacy supplement for Mifeprex was approved) through September 30, 2021.<sup>80</sup> Published studies have described alternatives in location and method for dispensing mifepristone by a certified prescriber (or equivalent healthcare provider in countries other than the United States). Some studies have examined replacing in-person dispensing in certain healthcare settings with dispensing at retail pharmacies<sup>81</sup>

<sup>79</sup> See 21 CFR 314.98, 21 CFR 314.80, and 21 CFR 314.81.

<sup>80</sup> In support of your request that we retain the REMS and continue limiting the dispensing of Mifeprex to patients in clinics, medical offices, and hospitals by or under the supervision of a certified prescriber, you reference two studies that you assert do not comply with the REMS (Petition at 19-22). Outcomes from both of the studies you reference have been reported in the published literature and are addressed in the discussion that follows. We note that as a general matter, a clinical investigation of an approved drug that is subject to a REMS can take place in healthcare settings outside those provided for in the REMS. When an approved drug that is subject to a REMS is studied in a clinical trial, the REMS does not apply to the use of the drug in that clinical trial. However, FDA reviews the protocol to ensure that it will be conducted in a manner that adequately addresses the risks that the REMS is intended to mitigate, such that the trial participants will not be exposed to an unreasonable and significant risk of illness or injury. See 21 CFR 312.42(b)(1)(i) and (b)(2)(i).

<sup>81</sup> Grossman D, Baba CF, Kaller S, et al. Medication Abortion With Pharmacist Dispensing of Mifepristone. *Obstet Gynecol* 2021;137:613–22; Rocca CH, Puri M, et al. Effectiveness and safety of early medication

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and dispensing mifepristone from pharmacies by mail.<sup>82</sup> Other studies have evaluated two modes of dispensing by prescribers: (1) prescribers mailing the medications to patients,<sup>83</sup> and (2) prescribers using couriered delivery of medications.<sup>84</sup> Different studies have evaluated dispensing mifepristone by mail by an entity described as “a partner organization.”<sup>85</sup>

We note that the ability to generalize the results of these studies to the United States population is hampered by differences between the studies with regard to pre-abortion care (e.g., telemedicine versus in-person). In addition, the usefulness of the studies is limited in some instances by small sample sizes and lack of follow-up information on outcomes with regard to both safety and efficacy. There are also factors which complicate the analysis of the dispensing element alone. Some of these factors are: (1) only a few studies have evaluated alternatives for in-person dispensing of mifepristone in isolation (for example, most studies on mail dispensing of mifepristone also include telemedicine consultation); and (2) because most serious adverse events with medical abortion are infrequent, further evaluation of changes in dispensing would require studies with larger numbers of participants. We did not find any large clinical studies that were designed to collect safety outcomes in healthcare systems similar to the United States. Despite the limitations of the studies we reviewed, we have concluded that overall the outcomes of these studies are not inconsistent with our conclusion that, based on the 1<sup>st</sup> year REMS assessment report and postmarketing safety data, mifepristone will remain safe and efficacy will be maintained if the in-person dispensing requirement is removed from the Mifepristone REMS Program.

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abortion provided in pharmacies by auxiliary nurse-midwives: A non-inferiority study in Nepal. *PLoS ONE* 13(1): e0191174. <https://doi.org/10.1371/journal.pone.0191174>; Wiebe ER, Campbell M, et al. Comparing telemedicine to in-clinic medication abortions induced with mifepristone and misoprostol. *Contracept X*. 2020; 2: 100023.

<sup>82</sup> Grossman D, Raifman S, Morris N, et.al. Mail-order pharmacy dispensing of mifepristone for medication abortion after in-person clinical assessment. *Contraception* 2021, ISSN 0010-7824, <https://doi.org/10.1016/j.contraception.2021.09.008>, Available online 20 September 2021; Upadhyay UD, Koenig LR, Meckstroth KR. Safety and Efficacy of Telehealth Medication Abortion in the US During the COVID-19 Pandemic. *JAMA Network Open*. 2021;4(8):e2122320, doi:10.1001/jamanetworkopen.2021.22320; Hyland P, Raymond EG, Chong E. A direct-to-patient telemedicine abortion service in Australia: Retrospective analysis of the first 18 months. *Aust N Z J Obstet Gynaecol* 2018;58: 335-340.

<sup>83</sup> See Anger HA, Raymond EG, et al. Clinical and service delivery implications of omitting ultrasound before medication abortion provided via direct-to-patient telemedicine and mail. *Contraception* 2021 Jul 28;S0010-7824(21)00342-5. doi: 10.1016/j.contraception.2021.07.108. Published online. Raymond E, Chong E, et al. TelAbortion: evaluation of a direct to patient telemedicine abortion service in the United States. *Contraception* 2019; 100:173-177. See also Chong et al., *infra* n. 103 Kerestes et al., *infra* n. 105, and Aiken et al., *infra* n. 106.

<sup>84</sup> Reynolds-Wright JJ, et al. *BMJ Sex Reprod Health* 2021;0:1–6. doi:10.1136/bmjsex-2020-200976.

<sup>85</sup> Endler M, Beets L, Gemzell Danielsson K, Gomperts R. Safety and acceptability of medical abortion through telemedicine after 9 weeks of gestation: a population-based cohort study. *BJOG* 2019;126:609-618. Norten H, Ilozumba O, Wilkinson J, Gemzell Danielsson K, Gomperts R. 10-year evaluation of the use of medical abortion through telemedicine: a retrospective cohort study. *BJOG* 2021; <https://doi.org/10.1111/1471-0528.16765>; Aiken ARA, Digol I, Trussell J, Gomperts R. Self-reported outcomes and adverse events after medical abortion through online telemedicine: population based study in the Republic of Ireland and Northern Ireland. *BMJ* 2017;357:j2011 <http://dx.doi.org/10.1136/bmj.j2011>.



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Below is a summary of our review of the literature, organized by the methods of dispensing mifepristone that were studied.

(a) Retail pharmacy dispensing

Three studies reported medical abortion outcomes for retail pharmacy dispensing of mifepristone after clinical evaluation (Grossman,<sup>86</sup> Rocca,<sup>87</sup> Wiebe<sup>88</sup>). Grossman conducted a US-based study in which mifepristone and misoprostol were dispensed from a pharmacy partnered with the clinic. Complete abortion without additional procedures occurred in 93.5 percent of participants with known outcomes. The reported proportion of complete abortion is within the range described in the approved mifepristone labeling. No participants experienced a serious adverse event, were hospitalized or required transfusion. Three participants had emergency department (ED) visits with treatment (intravenous hydration, pain medication, pelvic infection after uterine aspiration for incomplete abortion). The study safety and efficacy outcomes are consistent with labeled outcome frequencies. The study has limited generalizability because it was conducted in two US states and involved partnered pharmacies, some of which were in the same building as the clinic. Additionally, all participating pharmacies in this study were required to have a pharmacist on duty during clinic hours who had been trained in the study protocol and was willing to dispense mifepristone. The study conditions may not be generalizable to United States retail pharmacies; there is insufficient information to assess this.

Rocca<sup>89</sup> conducted an observational study evaluating participants who obtained medical abortions in Nepal by comparing the provision of medical abortion service by newly trained nurse midwives in pharmacies to medical abortion provided in government-certified clinics. The authors reported that, with respect to complete abortion (greater than 97 percent) and complications (no hospitalizations or transfusions), evaluation and dispensing in pharmacy was non-inferior to in-clinic evaluation and dispensing.

Wiebe,<sup>90</sup> in a retrospective, chart review study conducted in Canada, compared abortion outcomes of women who underwent medical abortion with telemedicine consult, and either received medications by courier or picked them up at a local pharmacy, with outcomes of a matched control cohort of women who received the medications at a pharmacy after an in-clinic visit. The groups had similar documented complete medical abortion outcomes (equal to or greater than 95 percent participants with known outcomes). The telemedicine group had one case of hemorrhage (0.5 percent) and one case of infection requiring antibiotics (0.5 percent) compared with no cases of hemorrhage or infection requiring antibiotics in the in-clinic cohort. The telemedicine group had more ED visits (3.3 percent compared to 1.5 percent in-clinic cohort). Both models of dispensing mifepristone resulted in efficacy and safety outcomes within labeled frequency.

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<sup>86</sup> Grossman et al., *supra* n. 81.

<sup>87</sup> Rocca et al., *supra* n. 81.

<sup>88</sup> Wiebe et al., *supra* n. 81.

<sup>89</sup> Rocca et al., *supra* n. 81.

<sup>90</sup> Wiebe et al., *supra* n. 81.



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None of the three studies allow a determination regarding differences in safety between in-person dispensing by a certified prescriber in a health care setting and dispensing through a retail pharmacy, due to limitations on the generalizability of the results of the studies to the current retail pharmacy environment in the United States. The outcome findings from the one United States study (Grossman)<sup>91</sup>, in which the pharmacies were partnered with prescribers, are unlikely to be broadly generalizable to the current retail pharmacy environment and do not reflect typical prescription medication availability with use of retail pharmacy dispensing. For the retail pharmacy dispensing study in Canada (Wiebe),<sup>92</sup> timely provision of medication from the retail pharmacy was accomplished by either courier to the woman or faxed prescription to the woman's pharmacy. It is unknown whether conditions that would allow timely access to medications for medical abortion would occur in retail pharmacies throughout the United States, suggesting the findings from that study may not be broadly generalizable. The third study (Rocca)<sup>93</sup> evaluated medical abortion provided in Nepali pharmacies and essentially moved the abortion provider and clinical examination into the pharmacy, a scenario that is not, at this time, applicable to the United States retail setting.

(b) Mail order pharmacy

Three studies evaluated mail order pharmacy dispensing (Grossman,<sup>94</sup> Upadhyay,<sup>95</sup> Hyland<sup>96</sup>). Grossman published an interim analysis of an ongoing prospective cohort study evaluating medical abortion with mifepristone and misoprostol dispensed by mail-order pharmacy after in-person clinical assessment. Complete abortion without additional procedures occurred in 96.9 percent of participants with known outcomes. Two (0.9 percent) participants experienced serious adverse events; one received a blood transfusion and one was hospitalized overnight. Nine (4 percent) participants attended 10 ED visits. In this interim analysis, the outcomes are consistent with labeled frequencies.

Upadhyay<sup>97</sup> reports findings from a retrospective cohort study of women undergoing medical abortion in the United States without a consultation or visit. Eligibility was assessed based on a participant-completed online form collecting pregnancy and medical history. Participants who were considered eligible received medication delivered by a mail-order pharmacy. Abortion outcome was determined by either an assessment on day 3 or a 4-week pregnancy test. The investigators reported a complete abortion rate without additional procedures of 95 percent for participants with known outcomes and stated that no participants had any major adverse events. The proportion of abortion outcomes assessed at 3 days versus 4 weeks is not reported. Regardless, determining outcomes at 3 days is insufficient to determine outcome rates or safety findings because a 3-day follow-up period is too short. As recommended in Section 2.3 of the approved labeling, follow-up at

<sup>91</sup> Grossman et al., supra n. 81.

<sup>92</sup> Wiebe et al., supra n. 81.

<sup>93</sup> Rocca et al., supra n. 81.

<sup>94</sup> Grossman et al, supra n. 82.

<sup>95</sup> Upadhyay et al., supra n. 82.

<sup>96</sup> Hyland et al., supra n. 82.

<sup>97</sup> Upadhyay et al., supra n. 82.

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7-14 days after administration of mifepristone is more appropriate to evaluate safety and efficacy. This study used a model with numerous deviations from standard provision of medical abortion in the United States, such as no synchronous interaction with the prescriber during informed consent or prior to prescribing medication and no confirmation of self-reported medical, surgical, and menstrual history. These deviations, limited follow-up information, and small sample size limit the usefulness of this study.

Hyland<sup>98</sup> describes findings from a cohort study in Australia evaluating medical abortion outcomes utilizing telemedicine and a central mail order pharmacy. Complete abortions without additional procedures occurred in 96 percent of participants with documented outcomes and is consistent with labeled efficacy. Of the participants included in the analysis, 95 percent had no face-to-face clinical encounters after medications were mailed while 3 percent were admitted to the hospital and 2 percent had an outpatient encounter. One participant who was hospitalized and underwent a surgical uterine evacuation received a transfusion. Not included in the findings are 7 hospitalizations occurring in 7 participants who did not have “full follow up.” The authors do not report any other adverse events and conclude use of the telemedicine medical abortion service is safe. However, the reasons for hospitalization are not discussed by the authors; therefore, it is unknown why the patients were hospitalized. Although the reported frequency of hospitalizations (3 percent) is higher than the less than 1 percent in the FDA-approved mifepristone labeling, conclusions on the safety findings cannot be made in the absence of information about the reasons for hospitalization. Other limitations of this study include incomplete information about outcomes with face-to-face encounters.

Overall, the three studies evaluating mail order pharmacy dispensing suggest that efficacy of medical abortion is maintained with mail order pharmacy dispensing. With respect to safety, in the Grossman study<sup>99</sup> the interim analysis, although small, does not raise serious safety concerns. Safety findings from the Hyland<sup>100</sup> study are difficult to interpret. Although only one transfusion is reported and the authors state the findings demonstrate safety, a higher hospitalization rate and lack of information on the reasons for hospitalization preclude reaching any conclusions about the safety findings. Lastly, the Upadhyay<sup>101</sup> study had no reported adverse events, but the findings are less useful because of the limited follow-up, and because medical abortions were provided using a model with numerous deviations from standard provision of medical abortion in the United States.

#### (c) Clinic dispensing by mail

A total of five studies evaluated clinic dispensing by mail. Gynuity Health Projects conducted a prospective cohort study (the “TelAbortion” study) evaluating use of telemedicine for remote visits and mifepristone being dispensed from clinics via overnight or regular tracked mail. Three publications reviewed have reported outcomes for the Gynuity population exclusively: Raymond (outcomes from May 2016 to December

<sup>98</sup> Hyland et al., supra n. 82.

<sup>99</sup> Grossman et al., supra n. 82.

<sup>100</sup> Upadhyay et al., supra n. 82.

<sup>101</sup> Hyland et al., supra n. 82.

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2018),<sup>102</sup> Chong (outcomes from May 2016 to September 2020)<sup>103</sup> and Anger (outcomes from March 2020 to September 2020).<sup>104</sup> A fourth study, Kerestes,<sup>105</sup> reports outcomes of medical abortion at the University of Hawai'i from April 2020 to November 2020 and a fifth study, Aiken (2021)<sup>106</sup> reports outcomes of medical abortion up to 70 days gestational age in the United Kingdom before and during the COVID-19 PHE in a retrospective cohort study.

In Raymond,<sup>107</sup> complete abortion without additional procedures occurred in 93 percent of participants with known outcomes. There were two hospitalizations (one participant received a transfusion for severe anemia despite having had a complete abortion) and 7 percent of participants had clinical encounters in ED/urgent care centers. The reported outcomes are similar to outcomes described in approved labeling except the combined ED/urgent care center encounters (7 percent) exceeded the ED visits in approved labeling (2.9-4.6 percent).<sup>108</sup> Of note, the authors state that half of the ED/urgent care visits did not entail any medical treatment. In Chong,<sup>109</sup> approximately 50 percent of the medical abortions occurred during the period of the COVID-19 PHE. Complete abortion without an additional procedure occurred in 95 percent of those with known outcomes. Transfusions were 0.4 percent and hospitalizations were 0.7 percent; 6 percent of participants had unplanned clinical encounters in ED/urgent care. Surgical interventions were required in 4.1 percent to complete abortion. The reported outcomes in Chong (which updated the findings described in Raymond) are similar to outcomes described in approved labeling except that (as with the Raymond study it updated) the combined ED/urgent care center encounters (6 percent) exceeded the ED visits in approved labeling (2.9-4.6 percent).

Anger,<sup>110</sup> which compared outcomes among participants enrolled in the Gynuity study who did ("test medical abortion cohort") versus did not ("no-test medical abortion cohort")<sup>111</sup>

<sup>102</sup> Raymond et al., *supra* n. 83.

<sup>103</sup> Chong E, Shochet T, et al. Expansion of a direct-to-patient telemedicine abortion service in the United States and experience during the COVID-19 pandemic. *Contraception* 2021;104:43-48.

<sup>104</sup> Anger et al., *supra* n. 83.

<sup>105</sup> Kerestes C, Murayama S, et al. Provision of medication abortion in Hawai'i during COVID-19: Practical experience with multiple care delivery models. *Contraception* 2021 Jul;104(1):49-53. doi:10.1016/j.contraception.2021.03.025. Epub 2021 Mar 28.

<sup>106</sup> Aiken ARA, Lohr PA, et al. Effectiveness, safety and acceptability of no-test medical abortion (termination of pregnancy) provided via telemedicine: a national cohort study. *BJOG* 2021;128:1464-1474.

<sup>107</sup> Raymond, *supra* n. 83.

<sup>108</sup> The authors reported the combined frequency of emergency department/urgent care visits, whereas the approved labeling includes the frequency for emergency department (emergency room) visits. Therefore it is unknown whether the frequency of emergency department visits in the trial, as distinct from the combined frequency of emergency department/urgent care visits, is comparable to the frequency of emergency department visits reflected in approved labeling.

<sup>109</sup> Chong et al., *supra* n. 103.

<sup>110</sup> Anger et al., *supra* n. 83.

<sup>111</sup> "No-test medication abortion" refers to medical abortion provided without a pretreatment ultrasound, pelvic examination or laboratory tests when, in the judgment of the provider, doing so is medically appropriate (appropriateness based on history and symptoms); "no-test medication abortion" does include post-abortion follow up. A sample protocol is described by Raymond et al." (Raymond EG, Grossman D, Mark A, et.al. Commentary: No-test medication abortion: A sample protocol for increasing access during a pandemic and beyond. *Contraception* 2020;101:361-366)

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have confirmation of gestational age/intrauterine location with an examination or ultrasound, found that those without an examination or ultrasound prior to medical abortion were more likely to require procedural interventions and had more unplanned clinical encounters.<sup>112</sup> There were no reported ectopic pregnancies in either group. The number of ED/urgent care visits and the proportion of unplanned clinical encounters that led to medical treatment were not reported. In the “test” group, complete medical abortion was confirmed in 98 percent of participants with known outcomes; one participant was “hospitalized and/or blood transfusion” and 8 percent had an unplanned clinic encounter (participant sought in-person medical care related to abortion and the visit was not planned prior to abortion). In the “no-test” group, complete medical abortion was confirmed in 94 percent of participants with known outcomes; two participants were “hospitalized and/or blood transfusion” and 12.5 percent had an unplanned clinical encounter.

Kerestes<sup>113</sup> included three different delivery models: traditional in-person visits, telemedicine consultation with in-person pick-up of medications, and telemedicine consultation with delivery of medications by mail (most of the latter were enrolled through Gynuity’s TelAbortion study). Among participants with follow-up data, the rates of successful medical abortion without surgery were consistent with outcomes in approved labeling. Blood transfusion was given to two participants (both in the telemedicine plus in-person pickup group). Although ED visits occurred the most frequently in the telemedicine plus mail group (four participants or 5.8 percent) and the least in the in-person group (two participants or 2.1 percent), the study reported no increases in other serious adverse events. Aiken (2021)<sup>114</sup> reported outcomes before and during the pandemic in a retrospective cohort study in the United Kingdom. The study compared the two cohorts: one before the pandemic with in-person visits and dispensing (traditional model) and one during the pandemic with either an in-person visit and in-person dispensing or a telemedicine visit and dispensing by mail or picked up from the clinic (hybrid model). Complete abortion occurred in greater than 98 percent in both cohorts; the rate was slightly higher in the telemedicine group than in the in-person group. There were no significant differences in the rates of reported serious adverse events. The investigators’ analysis determined that the efficacy and safety were comparable between both cohorts and concluded the hybrid model for medical abortion is effective and safe.

Taken together, data from the three Gynuity study reports (Raymond, Chong, and Anger), Kerestes, and Aiken (2021) support that efficacy of medical abortion was maintained when mifepristone was dispensed by mail from the clinic. Study reports of Raymond, Chong, and Kerestes all suggest there may be an increase in ED/urgent care visits with telemedicine visits and dispensing by mail from the clinic, but without increases in other serious adverse events. Anger’s comparative analysis suggests a pre-abortion examination may decrease the occurrence of procedural intervention and decrease the number of unplanned visits for postabortion care. The Aiken (2021) study appears to be of sufficient

<sup>112</sup> We note that the two cohorts were not randomized in the Anger study; they had different baseline characteristics. Consequently, findings based on the comparisons between the two cohorts should be interpreted carefully.

<sup>113</sup> Kerestes et al., *supra* n. 105.

<sup>114</sup> Aiken et al., *supra* n. 106.

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sample size to determine whether safety outcomes with mail dispensing differ from in-person dispensing; however, significant limitations include that the analysis was based on deidentified information and the investigators were unable to verify the outcomes extracted. Further, the study's design did not capture all serious safety outcomes, thus limiting the certainty of the findings.

Notwithstanding the limitations discussed above, these studies overall support that dispensing by mail from the clinic is safe and effective. Although the literature suggests there may be more frequent ED/urgent care visits related to the use of mifepristone when dispensed by mail from the clinic, there are no apparent increases in other serious adverse events related to mifepristone use.

(d) Clinic dispensing by courier

Reynolds-Wright<sup>115</sup> reported findings from a prospective cohort study of participants at less than 12 weeks gestational age in Scotland undergoing medical abortion at home that provided mifepristone for pick up at the service or by couriered delivery to woman's home. The outcomes from this study in Scotland are consistent with the outcomes in the approved mifepristone labeling. However, the number of couriered deliveries was not reported. Thus this study does not provide abortion outcomes separately for couriered delivery of mifepristone and misoprostol. The study shares the same limitations as the Aiken (2021) study; the study's design did not capture all serious safety outcomes, thus limiting the certainty of the findings.

(e) Partner organization dispensing by mail

Women on Web (WoW), an internet group, connects patients and providers outside of the US and provides medical abortion globally, dispensing mifepristone through "a partner organization" by mail. WoW uses a model with numerous deviations from the standard provision of medical abortion in the United States. For example, this model has no synchronous interaction with the prescriber during informed consent or prior to prescribing medication and no confirmation of self-reported medical, surgical, and menstrual history or confirmed pregnancy testing. Three studies (Endler, Norten, and Aiken (2017))<sup>116</sup> reported outcomes based on dispensing through this model. Endler and Norten reported outcomes from WoW cohorts but do not provide relevant information on mifepristone dispensing by mail because neither provide meaningful outcomes data for consideration. Although Aiken (2017) is a large cohort study, the outcomes are self-reported and an unusually high rate of outcomes are unaccounted for; these limitations result in the data being insufficient to determine the safety of dispensing mifepristone by mail through a partner organization.

In sum, there are insufficient data from the literature we have reviewed to determine the safety and efficacy of dispensing from a retail pharmacy, by courier, or by a partner organization. With respect to dispensing mifepristone by mail, our review of the literature indicates that dispensing mifepristone by mail from the clinic or from a mail order

<sup>115</sup> Reynolds-Wright JJ, et al. *BMJ Sex Reprod Health* 2021;0:1–6. doi:10.1136/bmjsex-2020-200976.

<sup>116</sup> Endler et al., Norten et al., and Aiken et al., supra n. 85.



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pharmacy does not appear to jeopardize the efficacy of mifepristone for medical abortion. While the studies we reviewed are not adequate on their own to establish the safety of the model of dispensing mifepristone by mail, the safety and efficacy outcomes reported in these studies remain within the ranges labeled for the approved mifepristone products. Although the literature suggests there may be more frequent ED/urgent care visits related to the use of mifepristone when dispensed by mail from the clinic, there are no apparent increases in other significant adverse events related to mifepristone use.

Based on the REMS assessment data, FAERS data from the time period when the in-person dispensing requirement was not being enforced, and our review of the literature, we conclude that mifepristone will remain safe and effective if the in-person dispensing requirement is removed, provided all the other requirements of the REMS are met and pharmacy certification is added. Removing the in-person dispensing requirement will render the REMS less burdensome to healthcare providers and patients, and provided all other requirements of the REMS are met, including the additional requirement for pharmacy certification, the REMS will continue to ensure that the benefits of mifepristone for medical abortion outweigh the risks. Therefore, to reduce the burden imposed by the Mifepristone REMS Program, the REMS must be modified to remove the in-person dispensing requirement, which would allow, for example, dispensing of mifepristone by mail via certified prescribers or pharmacies, in addition to in-person dispensing in clinics, medical offices and hospitals as currently outlined in ETASU C.

In your Petition, you state that “[e]liminating or relaxing the REMS to facilitate Internet or telephone prescriptions would be dangerous to women and adolescent girls” and that “health care providers prescribing abortion-inducing drugs over the Internet or phone or before a patient is even pregnant cannot adequately evaluate patients for contraindications to the drugs” (Petition at 18-19).

We do not agree that eliminating the REMS requirement for the dispensing of Mifeprex in certain healthcare settings will be dangerous to patients, nor do we agree that doing so will affect the ability of healthcare providers to evaluate women for contraindications to mifepristone in a regimen with misoprostol for medical termination of intrauterine pregnancy through 70 days gestation. There are many factors that contribute to patient safety, including evaluation of a patient, informed consent, development of a follow-up plan, and provision of a contact for emergency care. All of these can occur in many types of healthcare settings. The evaluation of patients for contraindications to medical abortion does not necessarily require direct physical contact with the certified prescriber.

You also assert that telemedicine abortion absolves abortion providers of responsibility for the well-being of their patients (Petition at 19). We do not agree. Healthcare providers who prescribe mifepristone are responsible for the well-being of their patients regardless of mode of evaluation or dispensing of medication. The Agency agrees with the American Medical Association that a healthcare provider-patient relationship is entered when the “physician serves a patient’s medical needs;”<sup>117</sup> in the context of medical abortion, this

<sup>117</sup> See [www.ama-assn.org/delivering-care/ethics/patient-physician-relationships](http://www.ama-assn.org/delivering-care/ethics/patient-physician-relationships).



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healthcare provider-patient relationship continues until resolution of the pregnancy or transfer of care to another healthcare provider.<sup>118</sup>

We also note that patients who are not pregnant at the time of evaluation would not be appropriate candidates for being prescribed mifepristone for medical termination of pregnancy because they do not fulfill the approved indication of having an intrauterine pregnancy of up to 70 days gestation.

## 2. Other Safety Issues and Additional Studies

In support of your request that we retain the Mifeprex REMS, you cite the Council for International Organizations of Medical Sciences' (CIOMS) definition of "rare" to assert that because "about 1 out of 100 women" using Mifeprex and misoprostol require surgery, serious complications are common, not rare (Petition at 15-16).<sup>119</sup> Although we agree that certain elements of the Mifepristone REMS Program are necessary to assure the safe use of mifepristone, we do not agree with your assertion.

In the Petition, you state that the Medication Guide improperly downplays the risks of the use of Mifeprex in a regimen with misoprostol and you cite the Medication Guide as stating "'rarely, serious and potentially life-threatening bleeding, infections, and other problems can occur following . . . medical abortion.' Specifically, 'in about 1 out of 100 women [administered Mifeprex and misoprostol] bleeding can be so heavy that it requires a surgical procedure.'" (Petition at 15). Using these two separate statements in the Medication Guide, you argue that the CIOMS's definition of rare ("1 out of 1000") means that if 1 out of 100 women using Mifeprex in a regimen with misoprostol require surgery, serious complications are common, not rare. (Petition at 16). However, your reference to the two sentences in the Medication Guide conflates two different clinical scenarios: (1) the adverse event of serious and potentially life-threatening bleeding, and (2) treatment failure.

The first sentence you reference states: "Although cramping and bleeding are an expected part of ending a pregnancy, rarely, serious and potentially life-threatening bleeding, infections, or other problems can occur following a miscarriage, surgical abortion, medical abortion, or childbirth." This statement refers to life-threatening adverse events that can occur during termination regardless of gestational age or during miscarriage or childbirth regardless of the mode of delivery (e.g., vaginal delivery or cesarean section). At the time of our review of the clinical studies submitted to support the S-020 efficacy supplement, the reported rate of death in the studies reviewed, based on one death, was 0.007 percent (very rare under the CIOMS definition).<sup>120</sup> The rate of infections requiring hospitalization or

<sup>118</sup> See <https://www.ama-assn.org/delivering-care/ethics/ethical-practice-telemedicine>.

<sup>119</sup> Council for International Organizations of Medical Sciences. Guidelines for Preparing Core Clinical Safety Information on Drugs Second Edition. 1999. <https://cioms.ch/wp-content/uploads/2018/03/Guidelines-for-Preparing-Core-Clinical-Safety-Info-Drugs-Report-of-CIOMS-Working-Group-III-and-V.pdf>. Accessed December 13, 2021 (CIOMS).

<sup>120</sup> Id. at 36 (defining the "very rare" standard category of frequency as less than 0.01 percent).

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intravenous antibiotics was less than 0.1 percent (rare under the CIOMS definition),<sup>121</sup> and rates of transfusion were 0.03-0.7 percent (rare to uncommon under the CIOMS definition).<sup>122</sup> Therefore, “rarely” accurately refers to the frequency of the adverse events referenced in this statement.

The second sentence you reference from the Medication Guide states: “In about 1 out of 100 women, bleeding can be so heavy that it requires a surgical procedure (surgical aspiration or D&C).” This statement refers to the rate of surgical procedures for bleeding following treatment with mifepristone. Heavy bleeding or hemorrhage after medical abortion is a small subset of bleeding and can require a surgical procedure due to ongoing pregnancy or incomplete expulsion; these are considered failed treatment rather than adverse events and are not characterized using the CIOMS definitions. Even if heavy, bleeding after medical abortion may not be considered a serious adverse event unless clinically diagnosed as hemorrhage or requiring a transfusion. Furthermore, in the vast majority of medical abortions, surgical intervention is not necessary.

You also cite a 2009 study and a 2018 study to assert that medical abortions carry greater risks than surgical abortions (Petition at 16). The 2009 Niinimäki, et al.<sup>123</sup> study reported overall incidences of immediate adverse events (up to 42 days) in medical and surgical abortions performed in women undergoing induced abortion from 2000-2006 based on data from the Finnish national registries. We agree that the overall incidence of adverse events for medical abortion was fourfold higher when compared with surgical abortion (20.0 percent versus 5.6 percent). Specifically, the incidence of hemorrhage, incomplete abortion, and surgical (re)evacuation were higher for medical abortion. However, the authors specifically noted that because medical abortion is associated with longer uterine bleeding, the high rate of events, which were pulled from a national registry reflecting both inpatient and outpatient visits, is not surprising. They opined that uterine bleeding requiring surgical evacuation probably better reflects the severity of bleeding after termination of pregnancy; the incidence of such bleeding was relatively low, although it was more common with medical abortion. In addition, the authors acknowledged there are inherent weaknesses in registry-based studies; there is variable reliability both of diagnoses and of severity of diagnoses. Nevertheless, the authors concluded that both methods are generally safe and recommended discussing the adverse event profiles of different methods when counseling women seeking pregnancy termination.

We note that Ireland, et al.<sup>124</sup> reported findings from a more recent retrospective cohort study of 30,146 United States women undergoing pregnancy termination before 64 days of gestation from November 2010 to August 2013. Efficacy of pregnancy termination was 99.6 percent and 99.8 percent for medical and surgical abortion, respectively.

<sup>121</sup> Id. at 36 (defining the “rare” standard category of frequency as greater than or equal to 0.01 percent and less than 0.1 percent).

<sup>122</sup> Id. at 36 (defining the “uncommon” standard category of frequency as greater than or equal to 0.1 percent and less than 1 percent); see also 2016 Clinical Review, *supra* n. 13, at 47 and 51.

<sup>123</sup> Niinimäki M, Pouta A, Bloigu A, et al. Immediate complications after medical compared with surgical termination of pregnancy. *Obstet Gynecol.* 2009;114(4):795-804.

<sup>124</sup> Ireland LD, Gatter, M, Chen, A. 2015. Medical Compared with Surgical Abortion for Effective Pregnancy Termination in the First Trimester. *Obstetrics & Gynecology* 126;22-28.

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Unanticipated aspiration for persistent pain, bleeding or both were 1.8 percent and 0.4 percent for medical and surgical abortion respectively. These findings are compatible with the Niinimäki study findings. There was no difference in major adverse events as defined by the authors (emergency department visit, hospitalization, uterine perforation, infection, hemorrhage requiring transfusion) between the groups. The authors conclude medical and surgical abortion before 64 days of gestation are both highly effective with low complication rates.

The 2018 Carlsson study is addressed above in section II.A.2.b.ii. of this response; as discussed above, that study showed no statistically significant difference between the overall complication rates between an “at home” and “at the hospital” abortion.<sup>125</sup>

We acknowledge that medical abortion is known to have more days of bleeding and increased rates of incomplete abortion compared to surgical abortion. However, as noted above, in the vast majority of medical abortions, surgical intervention is not necessary. Thus, medical abortion and surgical abortion are two options; both have benefits, side effects, and potential complications. Patients and their healthcare providers should discuss which method is preferable and safer according to each woman’s unique situation.

You state that the Mifeprex REMS should require a formal study for at-risk populations, including: patients under the age of 18; patients with repeat Mifeprex abortions; patients with limited access to emergency room services; and patients who self-administer misoprostol (Petition at 13-14). As we explain below, additional studies are not needed at this time.

In justifying your assertion that a formal study is required in patients under the age of 18, you state that Mifeprex was approved for use in the pediatric population in 2000 after the requirement for studies in the pediatric population was waived (Petition at 13-14). The approved indication for mifepristone does not limit its use by age. Although patients age 17 and under were not included in the clinical trials supporting the initial approval of Mifeprex in 2000, we stated at the time that the safety and efficacy were expected to be the same for postpubertal (i.e., post-menarchal) adolescents. Our conclusion in 2000 that pediatric studies of Mifeprex were not needed for approval was consistent with FDA’s implementation of the regulations in effect at that time. Because we determined that there were sufficient data from studies of mifepristone, the original Mifeprex approval should have reflected the Agency’s conclusion that the pediatric study requirements were waived for pre-menarchal females and that the pediatric study requirements were met for post-menarchal adolescents, rather than stating that the Agency was waiving the requirements for all pediatric age groups.

As currently required by the Pediatric Research Equity Act (PREA),<sup>126</sup> certain applications or supplemental applications must include pediatric assessments of the safety and effectiveness of the drug for the claimed indication(s) in all relevant pediatric

<sup>125</sup> Carlsson et al., *supra* n. 49.

<sup>126</sup> Section 505B of the FD&C Act (21 U.S.C. 355c).

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subpopulations, unless that requirement is waived or deferred.<sup>127</sup> In accordance with PREA, when FDA reviewed the S-020 efficacy supplement, a partial waiver was granted for pediatric studies in pre-menarchal females because pregnancy does not occur in premenarchal females. We also determined that the applicant had fulfilled the pediatric study requirement in post-menarchal adolescents. This determination was based on data extrapolated from adults and information in literature. Review of these findings found the safety and efficacy in this population to be similar to the safety and efficacy in the adult population.<sup>128</sup> Therefore, we do not agree that a formal study is required in patients under 18.

With regard to your concerns about repeat abortions and your assertion that a study is necessary in this population, we acknowledge that published data concerning adverse reproductive health outcomes in U.S. women who undergo repeat medical abortions are limited. We concluded in our 2016 review of the S-020 efficacy supplement that there is no evidence that repeated medical or surgical abortion is unsafe or that there is a tolerance effect. We also noted that return to fertility after the use of mifepristone is well documented.<sup>129</sup> This is reflected both in Section 17 of the approved labeling, Patient Counseling Information, which states that the provider should “inform the patient that another pregnancy can occur following medical abortion and before resumption of normal menses,” and in the Medication Guide, which states “You can become pregnant again right after your pregnancy ends.” Although you state that more than one out of every three abortions in the United States is a repeat abortion (Petition at 14),<sup>130</sup> we are not aware of reports suggesting greater safety concerns in repeat abortions than a first-time abortion. Therefore, we do not agree that a study is necessary in this population. You also cite a published study, using a mouse model, of repeated medical termination of pregnancy that showed repeat medical abortion impaired the reproductive function of female mice (Petition at 14).<sup>131</sup> Per our 2016 review, there is no evidence in available clinical data that repeated medical or surgical abortion is unsafe, or that fertility is impaired by the use of mifepristone; therefore, data from a single non-clinical study in mice are not persuasive.<sup>132</sup>

With respect to your request for a formal study of mifepristone for medical abortion in women without access to emergency care, we disagree that such a study is necessary. In order to become a certified prescriber, a healthcare provider must agree that they have the ability to provide surgical intervention in cases of incomplete abortion or severe bleeding or have made plans to provide such care through others, and that they have the ability to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary. These prescriber qualifications ensure that mifepristone is prescribed to women for whom emergency care is available.

<sup>127</sup> Section 505B(a)(2) of the FD&C Act (21 U.S.C. 355c(a)(2)).

<sup>128</sup> 2016 Clinical Review, *supra* n. 13, at 74-76.

<sup>129</sup> *Id.* at 47.

<sup>130</sup> In support of this assertion, you cite Jones R, Jerman J, Ingerick M. Which abortion patients have had a prior abortion? Findings from the 2014 U.S. Abortion Patient Survey. *J Womens Health*.

<sup>131</sup> Lv F, Xu X, Zhang S, et al. Repeated abortion affects subsequent pregnancy outcomes in BALB/c mice. *PLoS One*. 2012;7(10):e48384. doi:10.1371/journal.pone.0048384.

<sup>132</sup> 2016 Clinical Review, *supra* n. 13, at 47.

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Finally, you assert that FDA should require a formal study in patients who self-administer misoprostol. As explained in section II.A.2.b.ii of this response, FDA conducted a literature review of self-administration of misoprostol at home as part of its review of the S-020 efficacy supplement and found no safety or efficacy concerns with home self-administration of misoprostol. Therefore, we disagree that a formal study is required in this population.

With regard to safety generally, in addition to the FAERS data provided above (see section II.B.1.c.ii. in this response), FDA routinely monitors adverse events reported to FAERS and published in the medical literature for mifepristone for medical termination of pregnancy through 70 days gestation. We have not identified any new safety concerns with the use of mifepristone for this indication.

### 3. Other Articles

In your Petition, you reference several documents that discuss alternative models of providing abortion medications and advocate for the lifting of the REMS on mifepristone (Petition at 23-24). You assert that these recent publications demonstrate how abortion advocates will continue to pressure FDA to eliminate the REMS and move towards over-the-counter access for Mifeprex.<sup>133</sup>


We agree that the overarching message in the publications you reference appears to be advocating self-management of medical abortion. Nonetheless, as discussed in this response, we have determined that the Mifepristone REMS Program continues to be necessary for the safe use of this drug product, with some modifications.

## III. CONCLUSION

For the reasons set forth above, we deny your request that FDA restore and strengthen elements of the Mifeprex regimen and prescriber requirements approved in 2000; and we grant in part and deny in part your request to retain the Mifepristone REMS Program. As with all approved drug products, we will continue to monitor the safety of mifepristone for the approved indication and take any appropriate actions.

Sincerely,

Patrizia A.  
Cavazzoni -S

 Digitally signed by Patrizia A.  
Cavazzoni -S  
Date: 2021.12.16 15:05:41 -05'00'

Patrizia Cavazzoni, M.D.  
Director  
Center for Drug Evaluation and Research

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<sup>133</sup> You also reference clinical trials relating to the use of mifepristone for spontaneous miscarriage management and question the results of studies related to this use (Petition at 16-18). The use of mifepristone for the management of early miscarriage is not an approved indication for this drug product and is outside the scope of the Mifepristone REMS Program. Therefore, we do not address it in this response.

# Exhibit 44

Questions and Answers on FDA's Adverse Event  
Reporting System (FAERS),  
<https://www.fda.gov/drugs/surveillance/questions-and-answers-fdas-adverse-event-reporting-system-faers>



## Questions and Answers on FDA's Adverse Event Reporting System (FAERS)

### What is FAERS?

The FDA Adverse Event Reporting System (FAERS) is a database that contains adverse event reports, medication error reports and product quality complaints resulting in adverse events that were submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation ([ICH E2B \(/drugs/guidances-drugs/international-council-harmonisation-efficacy\)](https://www.fda.gov/drugs/guidances-drugs/international-council-harmonisation-efficacy)). Adverse events and medication errors are coded using terms in the [Medical Dictionary for Regulatory Activities \(MedDRA\) \(/http://www.meddra.org/\)](https://www.meddra.org/). [↗ \(/http://www.fda.gov/about-fda/website-policies/website-disclaimer\)](https://www.fda.gov/about-fda/website-policies/website-disclaimer). terminology.

### How does FDA use the information in FAERS?

FAERS is a useful tool for FDA for activities such as looking for new safety concerns that might be related to a marketed product, evaluating a manufacturer's compliance to reporting regulations and responding to outside requests for information. The reports in FAERS are evaluated by clinical reviewers, in the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER), to monitor the safety of products after they are approved by FDA.

If a potential safety concern is identified in FAERS, further evaluation is performed. Further evaluation might include conducting studies using other large databases, such as those available in the [Sentinel System. \(/sentinel-initiative-transforming-how-we-monitor-product-safety\)](https://www.fda.gov/sentinel-initiative-transforming-how-we-monitor-product-safety). Based on an evaluation of the potential safety concern, FDA may take regulatory action(s) to improve product safety and protect the public health, such as updating a product's labeling information, restricting the use of the drug, communicating new safety information to the public, or, in rare cases, removing a product from the market.

### Who sends reports to FAERS?

Healthcare professionals, consumers, and manufacturers submit reports to FAERS. FDA receives voluntary reports directly from healthcare professionals (such as physicians, pharmacists, nurses and others) and consumers (such as patients, family members, lawyers and others). Healthcare professionals and consumers may also report to the products' manufacturers. If a manufacturer receives a report from a healthcare professional or consumer, it is required to send the report to FDA as specified by regulations.

### How can I report an adverse event or medication error to FDA?

The [MedWatch \(https://www.fda.gov/Safety/MedWatch/default.htm\)](https://www.fda.gov/Safety/MedWatch/default.htm) website provides information about voluntary and mandatory reporting (<https://www.fda.gov/Safety/MedWatch/HowToReport/default.htm>).

### Can mandatory reporters submit adverse events electronically?

Yes, the [FDA Adverse Events Reporting System \(FAERS\) Electronic Submissions \(/drugs/fda-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-electronic-submissions\)](https://www.fda.gov/drugs/fda-adverse-event-reporting-system-faers-electronic-submissions) website provides drug and therapeutic biological product manufacturers, distributors, packers, and other interested parties with information about FDA Adverse Event Reporting System (FAERS) electronic submissions and instructions on how to electronically submit post-marketing individual case safety reports (ICSRs), with and without attachments.

## Does FAERS data have limitations?

Yes, FAERS data does have limitations. First, there is no certainty that the reported event (adverse event or medication error) was due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Furthermore, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether an event will be reported, such as the time a product has been marketed and publicity about an event. There are also duplicate reports where the same report was submitted by a consumer and by the sponsor. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population. For more information, please refer to the question " [What points should I consider while viewing the dashboard content?](https://fis.fda.gov/extensions/fpdwidgets/2e01da82-13fe-40e0-8c38-4da505737e36.html#_Toc493751926) ([https://fis.fda.gov/extensions/fpdwidgets/2e01da82-13fe-40e0-8c38-4da505737e36.html#\\_Toc493751926](https://fis.fda.gov/extensions/fpdwidgets/2e01da82-13fe-40e0-8c38-4da505737e36.html#_Toc493751926))."

## Is FAERS data available to the public?

FAERS data is available to the public in the following ways:

- [FAERS dashboard \(/drugs/fda-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-public-dashboard\)](/drugs/fda-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-public-dashboard): a highly interactive web-based tool that allows for the querying of FAERS data in a user friendly fashion.
- [FAERS data files \(/drugs/fda-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-latest-quarterly-data-files\)](/drugs/fda-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-latest-quarterly-data-files): provides raw data consisting of individual case safety reports extracted from the FAERS database. A simple search of FAERS data cannot be performed with these files by persons who are not familiar with the creation of relational databases.
- Individual case safety reports from the FAERS database can also be obtained by sending a [Freedom of Information \(FOI\) request to FDA \(/how-make-foia-request\)](/how-make-foia-request).

## How do I find or confirm my report is in FAERS?

To confirm that your report is in FAERS, please send a [Freedom of Information \(FOI\) request to FDA \(/how-make-foia-request\)](/how-make-foia-request).

## What are the benefits of the FAERS public dashboard?

This tool makes the data easier to query and produces user-friendly information and charts. For example, users can view a summary of adverse event reports received from 1968 to the present or for a specific timeframe. In addition, users can search on a product of interest within a specific timeframe.

## Will there be a tutorial so I can learn how to use this database?

Yes, a [recorded webinar \(/about-fda/pharmacy-student-experiential-program/fda-drug-topics-fda-adverse-events-reporting-system-faers-public-dashboard-january-30-2018\)](/about-fda/pharmacy-student-experiential-program/fda-drug-topics-fda-adverse-events-reporting-system-faers-public-dashboard-january-30-2018) is available which reviews the capabilities, and limitations, of the FAERS public dashboard.

## Is the FAERS public dashboard accessible on an Android™ or iPhone®?

Yes, but the user interface layout may not be very user friendly. FDA will continue to work on the dashboard to make the user interface Android and iPhone friendly.

## Can I download my search results from the dashboard?

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Questions and Answers on FDA's Adverse Event Reporting System (FAERS) | FDA

Yes, you will be able to export a limited set of search data to an Excel® spreadsheet and then download it. FDA will still continue to provide the [FAERS Latest Quarterly Data Files \(/drugs/fda-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-latest-quarterly-data-files\)](#) online.

Note: The data fields listed on the FAERS Dashboard currently is a subset of the data fields available in the FAERS Quarterly Data files. Future release of the FAERS Dashboard plans to make the other data fields available. Also the data displayed in the FAERS Dashboard may not be identical to the data in the FAERS Quarterly Data files due to different data extraction dates.

## Where else can I find safety information?

- [Potential Signals of Serious Risks/New Safety Information Identified from the FDA Adverse Event Reporting System \(FAERS\): quarterly reports on potential serious side effects identified by FAERS. \(/drugs/fda-adverse-event-reporting-system-faers/potential-signals-serious-risksnew-safety-information-identified-fda-adverse-event-reporting-system\)](#).
- [Post-marketing Drug and Biologic Safety Evaluations \(/drugs/surveillance/postmarket-drug-and-biologic-safety-evaluations\)](#): provides summary information about ongoing and completed post-marketing safety evaluations of adverse experience reports made to FDA for New Drug Applications (NDAs) and Biologic License Applications (BLAs) approved since September 27, 2007.
- Center for Drug Evaluation and Research (CDER): [Drug Safety and Availability \(https://www.fda.gov/Drugs/DrugSafety/default.htm\)](#).
- [Post-market Drug Safety Information for Patients and Providers \(https://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/default.htm\)](#)
- [MedWatch: The FDA Safety Information and Adverse Event Reporting Program \(https://www.fda.gov/Safety/MedWatch/default.htm\)](#).

## How are versions of a case in FAERS handled?

Each unique submission of a case received is assigned a version number (for example, Case #1234567, version 1). The initial version received will be version 1. If a follow up is received on a previously submitted case, then that version of the case will be version 2, and so on. The latest version of a case represents the most current information about that case.

The data is updated quarterly.

## What points should I consider while viewing the dashboard content?

When you view the website output of reported reactions (side effects or adverse drug reactions) for a drug product, it is important to consider the following points:

- **Data Quality:** There are many instances of duplicative reports and some reports do not contain all the necessary information. Duplicate reporting occurs when the same report is submitted by the consumer and the sponsor. The information in FAERS evolves daily and the number of individual cases may increase or decrease. It is therefore possible that the information on this website may change over time.
- **Existence of a report does not establish causation:** For any given report, there is no certainty that a suspected drug caused the reaction. While consumers and healthcare professionals are encouraged to report adverse events, the reaction may have been related to the underlying disease being treated, or caused by some other drug being taken concurrently, or occurred for other reasons. The information in these reports reflects only the reporter's observations and opinions.

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Questions and Answers on FDA's Adverse Event Reporting System (FAERS) | FDA

- **Information in reports has not been verified:** Submission of a report does not mean that the information included in it has been medically confirmed nor it is an admission from the reporter that the drug caused or contributed the event.
- **Rates of occurrence cannot be established with reports:** The number of suspected reactions in FAERS should not be used to determine the likelihood of a side effect occurring. The FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, information in these reports cannot be used to estimate the incidence (occurrence rates) of the reactions reported.
- **Patients should talk to their doctor** before stopping or changing how they take their medications.
- **Patient Outcomes received in FAERS:** These data describe the outcome of the patient as defined in U.S. reporting regulations (21 CFR 310.305, 314.80, 314.98, 600.80). Serious means that one or more of the following outcomes were documented in the report: death, hospitalization, life-threatening, disability, congenital anomaly, and/or other serious outcome. Documenting one or more of these outcomes in a report does not necessarily mean that the suspect product(s) named in the report was the cause of the outcomes.

Importantly, the FAERS data by themselves are not an indicator of the safety profile of the drug.

# Exhibit 45

Kathi A. Aultman, et al., *Deaths and Severe Adverse Events after the use of Mifepristone as an Abortifacient from September 2000 to February 2019*, 26 Law & Medicine 3 (2021).

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# ***Deaths and Severe Adverse Events after the use of Mifepristone as an Abortifacient from September 2000 to February 2019***

Kathi A. Aultman M.D.,\* Christina A. Cirucci M.D.,  
Donna J. Harrison M.D.,\*\* Benjamin D. Beran M.D.,\*\*\*  
Michael D. Lockwood D.O.,\*\*\*\* Sigmund Seiler M.D.\*\*\*\*\*

**ABSTRACT: Objectives:** Primary: Analyze the Adverse Events (AEs) reported to the Food and Drug Administration (FDA) after use of mifepristone as an abortifacient. Secondary: Analyze maternal intent after ongoing pregnancy and investigate hemorrhage after mifepristone alone.

**Methods:** Adverse Event Reports (AERs) for mifepristone used as an abortifacient, submitted to the FDA from September 2000 to February 2019, were analyzed using the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAEv3).

**Results:** The FDA provided 6158 pages of AERs. Duplicates, non-US, or AERs previously published (Gary, 2006) were excluded. Of the remaining, there were 3197 unique, US-only AERs of which there were 537 (16.80%) with insufficient information to determine clinical severity, leaving 2660 (83.20%) Codable US AERs (Figure 1). Of these, 20 were Deaths, 529 were Life-threatening, 1957 were Severe, 151 were Moderate, and 3 were Mild.

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The deaths included: 9 (45.00%) sepsis, 4 (20.00%) drug toxicity/overdose, 1 (5.00%) ruptured ectopic pregnancy, 1 (5.00%) hemorrhage, 3 (15.00%) possible homicides, 1 (5.00%) suicide, 1 (5.00%) unknown (Table 1).

Retained products of conception and hemorrhage caused most morbidity. There were 75 ectopic pregnancies, including 26 ruptured ectopics (includes one death).

There were 2243 surgeries including 2146 (95.68%) D&Cs of which only 853 (39.75%) were performed by abortion providers.

Of 452 patients with ongoing pregnancies, 102 (22.57%) chose to keep their baby, 148 (32.74%) had terminations, 1 (0.22%) miscarried, and 201 (44.47%) had unknown outcomes.

Hemorrhage occurred more often in those who took mifepristone and misoprostol (51.44%) than in those who took mifepristone alone (22.41%).

**Conclusions:** Significant morbidity and mortality have occurred following the use of mifepristone as an abortifacient. A pre-abortion ultrasound should be required to rule out ectopic pregnancy and confirm gestational age. The FDA AER system is inadequate and significantly underestimates the adverse events from mifepristone.

A mandatory registry of ongoing pregnancies is essential considering the number of ongoing pregnancies especially considering the known teratogenicity of misoprostol.

At the very least, the FDA should reinstate the original 2011 REMS and strengthen the reporting requirements.

**Conflict of Interest Statement:** The authors did not report any potential conflicts of interest. Authors note that although Dr. Harrison is an associate editor for Issues in Law and Medicine, she recused herself from any involvement in the peer review process for this manuscript.

**Keywords:** Mifepristone, Mifeprex, RU-486, Misoprostol, Abortifacient, Medical Abortion, Abortion Pill, Medical Abortion Complications, No touch abortion, DIY Abortion, Self-Administered Abortion, Adverse Events, Adverse Event Reports, Post-marketing Surveillance, FAERS, Drug Safety, Emergency Medicine, FDA, REMS, Risk Evaluation Mitigation Strategy.

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## Introduction

The application for mifepristone (RU-486, RU-38486, Mifeprex) as an abortifacient was submitted to the Food and Drug Administration (FDA) in 1996 by the Population Council, which was given the manufacturing and distribution rights from Roussel Uclaf.<sup>1</sup> The Population Council partnered with Danco Laboratories, newly created in 1995, and gave them the manufacturing, marketing, and distribution rights. The FDA approved mifepristone in September 2000 under restricted distribution regulations (Subpart H) due to the FDA's conclusion that restrictions "on the distribution and use of mifepristone are needed to ensure safe use of this product."<sup>2</sup>

Included in these restrictions was the requirement that all serious Adverse Events (AEs), after the use of mifepristone as an abortifacient, be reported to the FDA by Danco as part of post-marketing surveillance. According to the FDA,<sup>3</sup> the purpose of such post-marketing surveillance includes identification of potential risks recognized after the time of approval, identification of unexpected deaths, causal attribution of AEs based on the product's known pharmacological action, and AEs for which a Risk Evaluation Mitigation Strategy (REMS) is intended to mitigate the risk.

In 2006, in response to the deaths of 4 women from a rare bacterial sepsis from *Clostridium sordellii* (*C. sordellii*), the FDA and CDC convened a workshop, during which mifepristone alteration of the immune system was detailed, and they concluded that such alteration could lead to impaired ability to respond to *C. sordellii* toxin.<sup>4</sup>

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<sup>1</sup> Citizen petition re: Request for Stay and Repeal of the Approval of Mifeprex (mifepristone) for the Medical Termination of Intrauterine Pregnancy through 49 Day's Gestation Final. Before the Department of Health and Human Services: Food and Drug Administration. AAPLOG. 2002. 7-10. Accessed November 13, 2020. [https://aaplog.wildapricot.org/resources/Documents/2002%20Aug%2020%20Citizen%20Petition\\_Mifeprex.pdf](https://aaplog.wildapricot.org/resources/Documents/2002%20Aug%2020%20Citizen%20Petition_Mifeprex.pdf)

<sup>2</sup> Center for Drug Evaluation and Research. Approval Letter for Mifeprex NDA 20-687. February 18, 2000. Food and Drug Administration. p 5. Accessed November 16, 2020. [https://www.accessdata.fda.gov/drugsatfda\\_docs/applletter/2000/20687approvable00.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/applletter/2000/20687approvable00.pdf)

<sup>3</sup> US Department of Health and Human Services, Food and Drug Administration Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research. Best Practices in Drug and Biological Product Postmarket Safety Surveillance for FDA Staff. November 2019. p 7-8. Accessed Jan 16 2021. <https://www.fda.gov/media/130216/download> p7-8

<sup>4</sup> Emerging Clostridial Disease Workshop: May 11, 2006, Atlanta, GA. Department of Health and Human Services, Centers for Disease Control and Prevention, Food and Drug Administration, National Institutes of Health. 2006. p. 109,110. Accessed November 13, 2020. <https://aaplog.wildapricot.org/resources/2006%20CDC%20FDA%20Clostridial%20Disease%20Transcript.pdf>

There is evidence that both mifepristone<sup>5,6,7</sup> and misoprostol<sup>8</sup> can suppress immune response to *C. sordellii* in animal models.

In response to the septic deaths, Planned Parenthood changed their off-label protocol from vaginal administration of misoprostol to buccal in 2006.<sup>9,10</sup> Yet, as we found in our analysis, sepsis deaths from *C. sordellii* and other bacteria continued to occur after 2007. All sepsis deaths occurred with either vaginal or buccal misoprostol, which were both off label routes of administration until the buccal route was authorized in 2016.<sup>11</sup>

In 2011, the FDA approved a Risk Evaluation and Mitigation Strategy (REMS) for Mifepristone incorporating the original restrictions.<sup>12</sup> In May 2015, Mifepristone's sponsor submitted a supplemental new drug application to the FDA to obtain approval to revise the drug's labeling, which the FDA approved in 2016.<sup>13,14</sup> The 2016 changes in the Regimen and Prescriber Agreement extended the original gestational age limit from 49 days to 70 days, changed the mifepristone dose from 600 mg to 200 mg orally, changed the misoprostol dose from 400 mcg orally on Day 3 to 800 mcg buccally on Day 2 or 3, allowed non-physicians to become prescribers, reduced the number of required office visits from 3 to just one initial office visit, and allowed a repeat dose of misoprostol if complete expulsion did not occur.<sup>15</sup> The prescriber agreement was changed so

<sup>5</sup> Emerging Clostridial Disease Workshop: May 11, 2006, Atlanta, GA. Department of Health and Human Services, Centers for Disease Control and Prevention, Food and Drug Administration, National Institutes of Health. 2006. p. 109, 110 Accessed November 13, 2020.

<https://aaplog.wildapricot.org/resources/2006%20CDC%20FDA%20Clostridial%20Disease%20Transcript.pdf>

<sup>6</sup> Webster JJ, Sternberg EM. Role of the hypothalamic-pituitary-adrenal axis, glucocorticoids and glucocorticoid receptors in toxic sequelae of exposure to bacterial and viral products. *J Endocrinol.* 2004;181(2):212, 213, 216, 217. doi.org/10.1677/joe.0.1810207

<sup>7</sup> Hawes AS, Rock CS, Keogh CV, Lowry SF, Calvano SE. In vivo effects of the antiglycorticoid RU 486 on glucocorticoid and cytokine responses to Escherichia coli endotoxin. *Infect Immun.* 1992;60(7):2645, 2646. doi:10.1128/IAI.60.7.2641-2647.1992

<sup>8</sup> Aronoff DM, Hao Y, Chung J, et al. Misoprostol impairs female reproductive tract innate immunity against *Clostridium sordellii*. *J Immunol.* 2008;180(12):8227-8229. <https://doi.org/10.4049/jimmunol.180.12.8222>

<sup>9</sup> Trussell J, Nucatola D, Fjerstad M, Lichtenberg, ES. Reduction in infection-related mortality since modifications in the regimen of medical abortion. *Contraception*, 2014;89(3):193-196. <https://doi.org/10.1016/j.contraception.2013.11.020>

<sup>10</sup> Fjerstad M, Trussell J, Sivin I, Lichtenberg, ES. Rates of Serious Infection after Changes in Regimens for Medical Abortion. *N Engl J Med.* 2009 July 9;361(2):148-149. July 9, 2009 *N Engl J Med* 2009; 361:145-151. doi:10.1056/NEJMoa0809146

<sup>11</sup> GAO-18-292 Revised Mifeprex Labeling: Food and Drug Administration Information on Mifeprex Labeling Changes and Ongoing Monitoring Efforts. Report to Congressional Requesters. Food and Drug Administration. 2018. p. 7. Published March 2018. Accessed November 13, 2020. <https://www.gao.gov/assets/700/690914.pdf>

<sup>12</sup> NDA 20-687 MIFEPREX (mifepristone) Tablets, 200 mg: Risk Evaluation and Mitigation Strategy (REMS). Food and Drug Administration. 2011. 1-11. Reference ID: 2957855. Published June 8, 2011. Accessed November 13, 2020. [https://www.accessdata.fda.gov/drugsatfda\\_docs/remis/Mifeprex\\_2011-06-08\\_Full.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/remis/Mifeprex_2011-06-08_Full.pdf)

<sup>13</sup> GAO-18-292 Revised Mifeprex Labeling: Food and Drug Administration Information on Mifeprex Labeling Changes and Ongoing Monitoring Efforts. Report to Congressional Requesters. Food and Drug Administration. 2018. p. 1. Published March 2018. Accessed November 13, 2020. <https://www.gao.gov/assets/700/690914.pdf>

<sup>14</sup> NDA 20-687 MIFEPREX (mifepristone) Tablets, 200 mg: Risk Evaluation and Mitigation Strategy (REMS). Food and Drug Administration. 2016. 1-8. Reference ID: 3909592. Published March 29, 2016. Accessed November 13, 2020. [https://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2016/020687Orig1s020RemsR.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/020687Orig1s020RemsR.pdf)

<sup>15</sup> GAO-18-292 Revised Mifeprex Labeling: Food and Drug Administration Information on Mifeprex Labeling Changes and Ongoing Monitoring Efforts. Report to Congressional Requesters. Food and Drug Administration. 2018. p.7. Published March 2018. Accessed November 13, 2020. <https://www.gao.gov/assets/700/690914.pdf>

that instead of being required to “report any hospitalization, transfusion or other serious event to Danco Laboratories,”<sup>16</sup> providers were only required to report deaths.<sup>17</sup> The requirement to report ongoing pregnancies that are not terminated was also eliminated. “The FDA approved GenBioPro, Inc.’s abbreviated new drug application (ANDA) for generic Mifeprex on April 11, 2019” and “established a single, shared system REMS for mifepristone products” without substantially changing the REMS.<sup>18</sup>

During the COVID-19 pandemic the Maryland District Court issued a preliminary injunction prohibiting the FDA from enforcing the in-person dispensing and signature requirements contained in the mifepristone REMS.<sup>19</sup> This decision eliminated the need for an initial office visit for dispensing the medication and opened the door for dispensing of the drug via telehealth with no actual clinician contact. On January 12, 2021, the Supreme Court enabled the FDA to enforce the mifepristone REMS.<sup>20</sup> These requirements are essential for the safety of women and must be kept in place.

The first systematic analysis of these Adverse Event Reports (AERs) obtained by the Freedom of Information Act (FOIA), was published by Gary and Harrison in 2006.<sup>21</sup> This paper extends that analysis to AERs not previously published and augments the scant published literature on mifepristone safety.

## Objectives

Primary: To analyze and codify the significant adverse events and their treatment after the use of mifepristone as an abortifacient, extending the previously published analysis by Gary in 2006.<sup>22</sup> Secondary: To examine maternal decisions in the case of ongoing pregnancy after attempted mifepristone termination, and to determine if failing to take misoprostol after mifepristone increased the risk of hemorrhage.

<sup>16</sup> NDA 20-687 MIFEPREX (mifepristone) Tablets, 200 mg: Risk Evaluation and Mitigation Strategy (REMS). Food and Drug Administration. 2011. p. 7. Reference ID: 2957855. Published June 8, 2011. Accessed November 13, 2020. [https://www.accessdata.fda.gov/drugsatfda\\_docs/remis/Mifeprex\\_2011-06-08\\_Full.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/remis/Mifeprex_2011-06-08_Full.pdf)

<sup>17</sup> NDA 20-687 MIFEPREX (mifepristone) Tablets, 200 mg: Risk Evaluation and Mitigation Strategy (REMS). Food and Drug Administration. 2016. p. 6. Reference ID: 3909592. Published March 29, 2016. Accessed November 13, 2020. [https://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2016/020687Orig1s020RemsR.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/020687Orig1s020RemsR.pdf)

<sup>18</sup> Questions and Answers on Mifeprex. Food and Drug Administration. March 28, 2018. Updated 4-12-2019. Accessed November 13, 2020. <https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/questions-and-answers-mifeprex>

<sup>19</sup> American College of Obstetricians and Gynecologists, et al., v. Food and Drug Administration, et al., No. 20-1320, 2020 WL 3960625 (D. Md. July 13, 2020). Accessed November 16th, 2020. <https://www.courthousenews.com/wp-content/uploads/2020/07/093111166803.pdf>

<sup>20</sup> FDA v ACOG. SCOTUS. 20a34\_3f14. Accessed January 20, 2021. [https://www.supremecourt.gov/opinions/20pdf/20a34\\_3f14.pdf](https://www.supremecourt.gov/opinions/20pdf/20a34_3f14.pdf)

<sup>21</sup> Gary M, Harrison D. Analysis of Severe Adverse Events Related to the Use of Mifepristone as an Abortifacient. *Ann Pharmacother*. 2006 Feb 40(2):191-7. <https://doi.org/10.1345/aph.1G481>

<sup>22</sup> Gary M, Harrison D. Analysis of Severe Adverse Events Related to the Use of Mifepristone as an Abortifacient. *Ann Pharmacother*. 2006 Feb 40(2):191-7. <https://doi.org/10.1345/aph.1G481>

## Materials and Methods

FDA AERs related to the use of mifepristone from September 2000 to February 2019 were obtained through the Freedom of Information Act (FOIA) from the FDA, and a comparison was made with FDA reports available online on the FDA Adverse Events Reporting System (FAERS) Dashboard.<sup>23</sup> Duplicate AERs were identified by comparing FDA case identification numbers, manufacturer identification numbers, dates of treatment, patient age, and descriptions of case scenarios to ensure that each case was included only once in this analysis. The authors excluded duplicates, cases originating outside of the United States, and cases previously published in the Gary analysis<sup>24</sup> (Figure 1).

One of the concerns in looking at AEs is the risk of falsely assigning causality. The FDA does not give guidance for determining causality for AEs in the AERs but does give guidance for selecting AEs for inclusion in the Adverse Reaction section of the Drug Label.<sup>25</sup> They recommend that, “Decisions on whether there is some basis to believe there is a causal relationship are a matter of judgment and are based on factors such as” the “frequency of reporting,” “the extent to which the adverse event is consistent with the pharmacology of the drug,” “the timing of the event relative to the time of drug exposure,” and other factors. Although a causal relationship cannot be attributed with certainty to all reported AEs for a drug, a causal relationship seems probable for each of the categories of AEs we chose to analyze based on these factors, except for ectopic pregnancies and some of the deaths. Ectopic pregnancies were included in our analysis not because there is a causal relationship, but because ectopic pregnancy is a contraindication to the use of mifepristone and the diagnosis was missed, putting women’s lives at risk. The deaths must be evaluated individually to determine causality.

Because reporting is often voluntary and sporadic, there is no denominator for how many mifepristone abortions are performed in the U.S. It was therefore impossible to calculate complication rates for mifepristone and misoprostol abortions based on AER data. For clarity, we specified the denominator used in each case. Coding for severity was done using the National Cancer Institute’s Common Terminology Criteria for Adverse Events (CTCAEv3),<sup>26</sup> since this was

<sup>23</sup> FDA Adverse Events Reporting System (FAERS) Public Dashboard. Food and Drug Administration. Accessed November 13, 2020. <https://fis.fda.gov/sense/app/d10be6bb-494e-4cd2-82e4-0135608ddc13/sheet/33a0f68e-845c-48e2-bc81-8141c6aaf772/state/analysis>

<sup>24</sup> Gary M, Harrison D. Analysis of Severe Adverse Events Related to the Use of Mifepristone as an Abortifacient. *Ann Pharmacother*. 2006 Feb 40(2):191-7. <https://doi.org/10.1345/aph.1G481>

<sup>25</sup> Guidance for Industry Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products — Content and Format. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER); January 2006. P. 8. Accessed January 8, 2021. <https://www.fda.gov/media/72139/download>

<sup>26</sup> Common Terminology Criteria for Adverse Events v3.0 (CTCAE). Cancer Center Therapy Evaluation Program (CTEP); 2003. 1-77. Published December 12, 2003. Accessed November 13, 2020. <https://aaplog.wildapricot.org/resources/CTCAEv3.pdf>



the methodology used in the original analysis of the first 607 Adverse Events.<sup>27</sup> The five levels of coding are: Mild, Moderate, Severe, Life-threatening, and Death.

Overall severity (Figure 1) for each unique AER was determined independently by two board-certified physicians (Obstetrics and Gynecology or Family Medicine). Since within each AER, a patient may have experienced several Adverse Events (AEs), the overall severity of the AER was based on the highest severity of its AEs. For the diagnoses we analyzed (Table 1), each AE was coded in the same manner and stratified according to type, severity, and treatment. Disagreements were resolved by discussion or review by a third board-certified Obstetrician-Gynecologist who also reviewed coding for uniformity. Surgeries, transfusions, providers, and location of treatment were analyzed and tabulated.

Ruptured ectopic pregnancies were coded as Life-threatening and unruptured ectopic pregnancies as Severe.

Infections were coded as Life-threatening when evidence of sepsis was present, or ICU-level treatment was required. They were coded as Severe if parenteral/IV antibiotics were given and Moderate if oral antibiotics were prescribed.

Life-threatening hemorrhage was defined, as in the previous analysis, to be transfusion of two or more units of packed red blood cells (PRBCs), hemoglobin less than 7, or documented large volume, rapid blood loss with clinical symptomatology of acute blood loss anemia (e.g., syncope, tachycardia, hypotension). Severe hemorrhage was defined as requiring surgical intervention and/or less than 2 U PRBCs. Moderate hemorrhage was defined as management with fluids/medication alone.

Retained Products of Conception (RPOC) was coded as Severe if a dilatation and curettage/evacuation (D&C) was performed. Ongoing viable intrauterine pregnancy was considered equivalent in severity to RPOC requiring curettage and thus Severe. When the ultimate outcome was unknown, the pregnancy was considered ongoing if “ongoing pregnancy” was noted or ultrasound showed cardiac motion or significant growth.

AEs which did not contain sufficient information to assign an accurate severity code were deemed “Uncodable.” AERs lacking any codable information were deemed overall Uncodable.

The percent of women with significant hemorrhage after mifepristone alone was compared to those who took both mifepristone and misoprostol, to investigate the validity of the assertion that lack of subsequent misoprostol administration was a causative factor in hemorrhage after mifepristone use.<sup>28</sup>

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<sup>27</sup> Gary M, Harrison D. Analysis of Severe Adverse Events Related to the Use of Mifepristone as an Abortifacient. *Ann Pharmacother*. 2006 Feb 40(2):191-7. <https://doi.org/10.1345/aph.1G481>

<sup>28</sup> Creinin MD, Hou MY, Dalton L, Steward R, Chen MJ. Mifepristone Antagonization With Progesterone to Prevent Medical Abortion: A Randomized Controlled Trial. *Obstet Gynecol*. 2020;135(1):158-165. doi:10.1097/AOG.0000000000003620



## Results

### ***Adverse Event Report Overall Severity***

Figure 1 summarizes the handling of the AERs provided by the FDA and their severity coding. The FDA provided 6158 pages of AERs. Of these, any duplicates, non-US, or AERs previously published in the Gary paper were excluded from the analysis. There were 3197 unique, US-only AERs of which 537 had insufficient information to determine clinical severity, leaving 2660 Codable US-only AERs. Of these, 20 were Deaths, 529 were Life-threatening, 1957 were Severe, 151 were Moderate, and 3 were Mild.

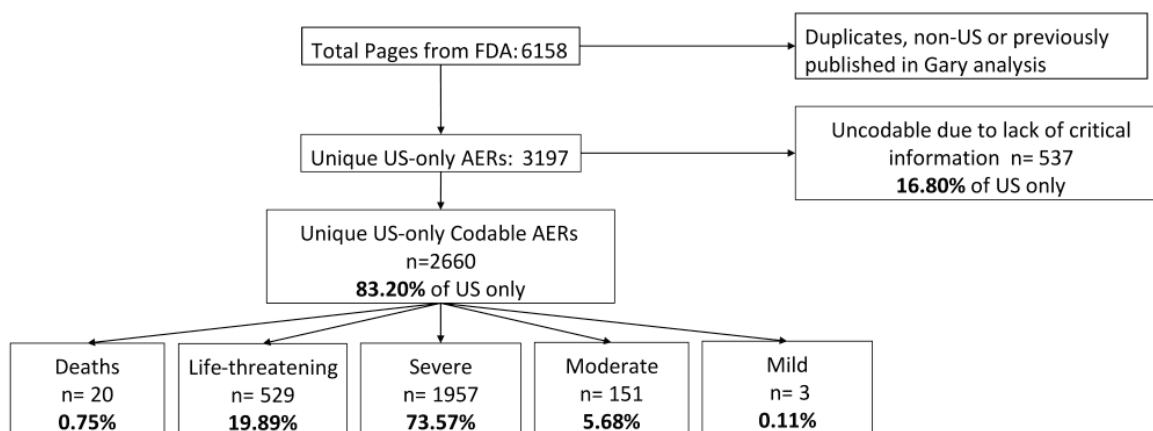
### ***Deaths (Table 1)***

Our analysis identified 23 of the 24 deaths reported by the FDA as of 2018.<sup>29</sup> Three of those deaths were previously published in the Gary paper<sup>30</sup> leaving 20 deaths (Table 1). Our analysis yielded a total of 7 sepsis deaths. These included five cases of *C. sordellii* and one case of *Clostridium perfringens*, all consistent with those reported by the FDA. There was an additional death which we categorized as a sepsis death whereas the FDA labeled this case as “delayed onset toxic shock-like syndrome” but did not include it as a sepsis death. The patient had an exploratory laparotomy revealing green pus, which was culture positive for *prevotella* and *peptostreptococcus*, and she died intraoperatively.<sup>31</sup>

<sup>29</sup> RCM # 2007-525 NDA 20-687 Mifepristone U.S. Post-Marketing Adverse Events Summary through 12/31/2018. FDA. 1-2. Reference ID: 4401215. Accessed November 13, 2020. <https://www.fda.gov/media/112118/download>

<sup>30</sup> Gary M, Harrison D. Analysis of Severe Adverse Events Related to the Use of Mifepristone as an Abortifacient. *Ann Pharmacother*. 2006 Feb 40(2):191-7. <https://doi.org/10.1345/aph.1G481>

<sup>31</sup> Individual Case Safety Report number 4734082-4-00-01. Danco Laboratories, LLC. Office of Post-marketing Drug Risk Assessment, Food and Drug Administration. Received August 4, 2005. Accessed November 13, 2020. <https://aaplog.wildapricot.org/resources/Peptostreptococcus%20death%209.10277-8.pdf>

**Figure 1. AER Distribution**

*Note:* From 2000 to 2016 FDA only required the manufacturer to report AEs which were severe, life-threatening or had fatal outcomes. Since 2016, FDA only requires the manufacturer to report fatal outcomes.

We categorized two deaths as suspicious for infectious death. One case was labeled by the FDA as “undetermined natural causes,” however, the AER reported the cause of death as “acute visceral and pulmonary (1420 grams) congestion and edema,”<sup>32</sup> which is consistent with the clinical findings for sepsis/Acute Respiratory Distress Syndrome (ARDS). This patient had autopsy-proven retained products of conception and blood cultures which grew *Strep viridans* isolated at less than 24 hours incubation. One additional case which the FDA labeled “methadone overdose”<sup>33,34</sup> we considered suspicious for sepsis. Prior to her death, this patient had fever and chills and was treated by an outside physician with cephalexin, which would have been ineffective against infections from *C. sordellii* or anaerobic gram-negative bacilli. There was no autopsy report or toxicology report in the AER.

Non-infectious deaths include one death that the FDA listed as “natural,” caused by “pulmonary emphysema.”<sup>35</sup> This patient was a 40-year-old chronic smoker who died within hours of misoprostol ingestion and had a contusion on her head consistent with a fall, a scenario possibly related to a cardiac event or acute respiratory reaction to misoprostol. She had an intact fetus at the time of

<sup>32</sup> Individual Case Safety Report number 9587011-03-00-01. Danco Laboratories, LLC. Office of Post-marketing Drug Risk Assessment, Food and Drug Administration. Received May 21, 2014. Accessed November 13, 2020. <https://aaplog.wildapricot.org/resources/death%20Visc%20pul%20cong.pdf>

<sup>33</sup> Individual Case Safety Report number 4970303-0-00-01. Danco Laboratories, LLC. Office of Post-marketing Drug Risk Assessment, Food and Drug Administration. Received April 21, 2014. Accessed November 13, 2020. <https://aaplog.wildapricot.org/resources/death%2023%20yo%20meth%20overdose%20fever%20and%20chills.pdf>

<sup>34</sup> Individual Case Safety Report number 5063156-8-00-01. Danco Laboratories, LLC. Office of Post-marketing Drug Risk Assessment, Food and Drug Administration. Received July 27, 2006. Accessed November 13, 2020. [https://aaplog.wildapricot.org/resources/methadone%20AER%20\(1\).pdf](https://aaplog.wildapricot.org/resources/methadone%20AER%20(1).pdf)

<sup>35</sup> Individual Case Safety Report number 11283049-02-00-01. Danco Laboratories, LLC. Office of Post-marketing Drug Risk Assessment, Food and Drug Administration. Received December 8, 2015. Accessed November 13, 2020. <https://aaplog.wildapricot.org/resources/emphysema.pdf>

autopsy. Other non-infectious deaths included one death from a ruptured ectopic pregnancy, one from hemorrhage, 3 possible homicides, one suicide, and 4 deaths from drug toxicity/overdose. It is unknown whether the 8 women who died by homicide, suicide, or drug toxicity/overdose were screened for domestic violence, drug addiction, or depression prior to the abortion.

### ***Infection (Table 1)***

Infection was the leading cause of mortality. There were 502 cases of infection, which included 9 Deaths, 39 had Life-threatening sepsis, 249 were Severe infections, 132 Moderate infections, and 73 infections which were Uncodable.

### ***Ectopic Pregnancy (Table 1)***

There were 75 ectopic pregnancies. Of these, 26 were ruptured, including 1 death. Twenty-four were unruptured, and there were 25 for which the rupture status was not given. Fifty-six ectopic pregnancies were treated surgically and 11 were treated with methotrexate. The management was not documented in 7 cases. The patient who died received no treatment as she died on the way to the hospital.

### ***Retained Products of Conception (RPOC) (Tables 1 and 2)***

RPOC was the leading cause of morbidity. There were 977 confirmed cases of RPOC, including 2 molar pregnancies, and 1506 likely cases of RPOC (documentation was inadequate for confirmation). Of the 2146 total D&Cs, most were for RPOC, including 897 for confirmed RPOC, 1058 for bleeding or presumed RPOC, but no pathology was provided, and 2 for molar pregnancy. A small percentage of RPOC had medical treatment or no treatment.

### ***Hemorrhage/Bleeding (Table 1)***

There were 1639 bleeding events including one death. These included 466 Life-threatening and 642 Severe events. There were also 106 events coded as Moderate, while 424 reports of bleeding were Uncodable given the information in the database.

### ***Ongoing Pregnancy (Table 1)***

There were 452 ongoing pregnancies. Of these 102 chose to keep their baby, 148 chose termination, 1 miscarried, and 201 had an unknown outcome. Of those with an unknown outcome, there were 44 patients referred or scheduled for termination, who did not follow through (39 no-showed, 3 canceled, 2 did not schedule).

***Surgeries (Table 2)***

There were 2243 surgeries including 2146 D&Cs, 76 laparoscopies/laparotomies without hysterectomy, 7 hysterectomies, and 14 other surgeries. Of the hysterectomies, 3 were performed for sepsis, 2 for hemorrhage, 1 for a cervical ectopic, and 1 for placenta accreta. There were 1291 surgeries performed in the hospital or ER and 952 in an outpatient setting. Of the 2146 D&Cs, 1194 were performed in the hospital or ER, and 952 in an outpatient setting. Of the 2146 D&Cs, 1194 were provided by the Hospital or ER, 853 by the abortion provider, and 99 by another outpatient provider.

***Transfusions (Table 2)***

Four hundred and eighty-one patients required blood transfusion following medical abortions. Of these, 365 received 1 to 10 units packed red blood cells (PRBCs) alone, 1 received fresh frozen plasma (FFP) alone, 8 received a combination of PRBCs and FFP, and 107 received an unknown amount of blood product.

***Relationship of Misoprostol Use to Hemorrhage (Table 3)***

The use of mifepristone with misoprostol was associated with a higher incidence of hemorrhage than the use of mifepristone alone. Of the 3056 women who took both mifepristone and misoprostol, 1572 (51.44%) hemorrhaged, whereas, among the 58 women who did not take misoprostol, only 13 (22.41%) hemorrhaged. It was unclear whether 84 patients took misoprostol or not. Fifty-four (64.29%) of them hemorrhaged. The hemorrhage rate was higher for the mifepristone with misoprostol group as compared to the mifepristone alone group even if all the unknowns were assigned to the mifepristone alone group or vice versa.

**Table 1 - Diagnoses<sup>a</sup>**

<b>Deaths</b>	<b>Deaths (n)</b>	<b>Deaths (%)</b>	<b>Deaths: % of (3197) Unique US AERs (%)</b>	<b>Organism (%)</b>
Sepsis	9	45.00%	0.28%	
Sepsis confirmed	7	35.00%	0.22%	100%
<i>Clostridium sordellii</i>	5	25.00%	0.16%	71.43%
<i>Clostridium perfringens</i> / <i>Peptostreptococcus</i>	1	5.00%	0.03%	14.29%
<i>Peptostreptococcus</i>	1	5.00%	0.03%	14.29%
Sepsis Likely, Unknown Organism	2	10.00%	0.06%	
<i>Visceral and Pulmonary Congestion consistent with ARDS / sepsis</i>	1	5.00%	0.03%	
<i>Fever / chills treated with cephalexin, found dead<sup>b</sup></i>	1	5.00%	0.03%	
Ruptured Ectopic Pregnancy	1	5.00%	0.03%	
Hemorrhage	1	5.00%	0.03%	
Possible Homicide	3	15.00%	0.09%	
Suicide	1	5.00%	0.03%	
Drug Toxicity/Overdose	4	20.00%	0.13%	
Unknown <sup>c</sup>	1	5.00%	0.03%	
<b>Total Deaths</b>	<b>20</b>	<b>100%</b>	<b>0.63%</b>	
<b>Infections, Level of Severity</b>	<b>Infections (n)</b>	<b>Infections (%)</b>	<b>Infections: % of (3197) Unique US AERs (%)</b>	
Death	9	1.79%	0.28%	
Life threatening infection/sepsis	39	7.77%	1.22%	
Severe infection (IV anitbiotics)	249	49.60%	7.79%	
Moderate infection (oral antibiotics)	132	26.29%	4.13%	
Uncodable <sup>d</sup>	73	14.54%	2.28%	
<b>Total Infections</b>	<b>502</b>	<b>100%</b>	<b>15.70%</b>	

**Table 1 – Diagnoses (Continued)**

<b>Ectopic Pregnancies, Rupture Status</b>	<b>Ectopic Pregnancies (n)</b>	<b>Ectopic Pregnancies (%)</b>	<b>Ectopic Pregnancies: % of (3197) Unique US AERs (%)</b>
Ruptured <sup>e</sup>	26	34.67%	0.81%
Unruptured <sup>f</sup>	24	32.00%	0.75%
Surgical Treatment	13	17.33%	0.41%
Methotrexate Treatment	11	14.67%	0.34%
Unknown Rupture Status <sup>g</sup>	25	33.33%	0.78%
Surgical Treatment	18	24.00%	0.56%
Unknown Treatment	7	9.33%	0.22%
<b>Total Ectopic Pregnancies</b>	<b>75</b>	<b>100%</b>	<b>2.35%</b>
<b>Ectopic Pregnancies, Level of Severity</b>	<b>Ectopic Pregnancies (n)</b>	<b>Ectopic Pregnancies (%)</b>	<b>Ectopic Pregnancies: % of (3197) Unique US AERs</b>
Death	1	1.33%	0.03%
Life Threatening (Ruptured, survived)	25	33.33%	0.78%
Severe (Not Ruptured)	24	32.00%	0.75%
Uncodable	25	33.33%	0.78%
<b>Total Ectopic Pregnancies</b>	<b>75</b>	<b>100%</b>	<b>2.35%</b>



**Table 1 – Diagnoses (Continued)**

<b>Retained Products of Conception (RPOC)</b>	<b>RPOC (n)</b>	<b>RPOC (%)</b>	<b>RPOC: % of (3197) Unique US AERs (%)</b>
RPOC confirmed	977	39.35%	30.56%
RPOC confirmed (by pathology or ultrasound); Had D&C	891	35.88%	27.87%
RPOC confirmed by U/S but D&C not documented	29	1.17%	0.91%
RPOC treated medically	27	1.09%	0.84%
Tissue at os (no D&C) <sup>h</sup>	27	1.09%	0.84%
Molar Pregnancy	2	0.08%	0.06%
No Treatment, RPOC on autopsy	1	0.04%	0.03%
RPOC Likely	1506	60.65%	47.11%
Had D&C, no pathology provided	1056	42.53%	33.03%
Unknown <sup>i</sup>	450	18.12%	14.08%
<b>Total RPOCs</b>	<b>2483</b>	<b>100%</b>	<b>77.67%</b>
<b>Bleeding Events, Level of Severity</b>	<b>Bleeding Events (n)</b>	<b>Bleeding Events (%)</b>	<b>Bleeding Events: % of (3197) Unique US AERs</b>
Death	1	0.06%	0.03%
Life threatening or Disabling: 2U or more transfusion or Hgb<7 or witnessed massive blood loss	466	28.43%	14.58%
Severe: surgical intervention and/or 1 U transfusion	642	39.17%	20.08%
Moderate: medical intervention	106	6.47%	3.32%
Uncodable <sup>j</sup>	424	25.87%	13.26%
<b>Total Bleeding Events</b>	<b>1639</b>	<b>100%</b>	<b>51.27%</b>

**Table 1 – Diagnoses (Continued)**

Ongoing Pregnancies, Outcome	Ongoing Pregnancies (n)	Ongoing Pregnancies	Ongoing Pregnancies: % of (3197) Unique US AERs (%)	Ongoing Pregnancies with Unknown Outcome (%)
Desired to Keep Pregnancy	102	22.57%	3.19%	
Kept Pregnancy	101	22.35%	3.16%	
Kept Pregnancy but baby died in-utero	1	0.22%	0.03%	
Terminated Pregnancy	148	32.74%	4.63%	
Surgical Termination <sup>k</sup>	139	30.75%	4.35%	
Medical Termination	9	1.99%	0.28%	
Unknown Intent, miscarried <sup>l</sup>	1	0.22%	0.03%	
Unknown Outcome	201	44.47%	6.29%	100%
Referred D&C but did not show	39	8.63%	1.22%	19.40%
Referred D&C but cancelled	3	0.66%	0.09%	1.49%
Told to schedule/referred D&C did not go	2	0.44%	0.06%	1.00%
Unknown outcome, no other information <sup>m</sup>	157	34.73%	4.91%	78.11%
<b>Total</b>	<b>452</b>	<b>100%</b>	<b>14.14%</b>	

<sup>a</sup> Because of rounding, percentages may not appear to add up exactly.

<sup>b</sup> FDA attributed to methadone overdose.

<sup>c</sup> 40 year old smoker died within hours of misoprostol ingestion. Per FDA, “natural causes due to severe pulmonary emphysema.”

<sup>d</sup> Patients with documented infection but inadequate information to determine severity.

<sup>e</sup> One of the ruptured ectopics died on the way to the hospital. The other 25 were treated surgically.

<sup>f</sup> The unruptured ectopics include two cornual ectopics, one treated surgically and one treated medically.

<sup>g</sup> Includes two cervical ectopics, one treated with D&C/Hysterectomy/massive transfusion and one with unknown treatment.

<sup>h</sup> Either with path provided, or described as RPOC, placental fragments, fetus, or tissue.

<sup>i</sup> Suspected RPOC indicating D&C needed, but not documented as being done.

<sup>j</sup> Patients with documented bleeding but inadequate information to determine severity.

<sup>k</sup> Includes one hysterotomy for pregnancy in non-communicating horn.

<sup>l</sup> After no show for surgical termination.

<sup>m</sup> Includes 10 with known gestational age 20-29 weeks.

**Table 2 – Treatment<sup>a</sup>**

Type of Surgery	Type of surgery (n)	Type of surgery (%)	Surgery: % of (3197) Unique US AERs (%)
<b>D&amp;C<sup>b</sup></b>	<b>2146</b>	<b>95.68%</b>	<b>67.13%</b>
<b>Hysterectomy</b>	<b>7</b>	<b>0.31%</b>	<b>0.22%</b>
Sepsis (includes 2 deaths)	3	0.13%	0.09%
Hemorrhage after uterine perforation	2	0.09%	0.06%
Hemorrhage - Cervical Ectopic	1	0.04%	0.03%
Placenta accreta	1	0.04%	0.03%
<b>Laparoscopy/Laparotomy without hysterectomy</b>	<b>76</b>	<b>3.39%</b>	<b>2.38%</b>
Ectopic (Actual or Suspected)	66	2.94%	2.06%
Infection	7	0.31%	0.22%
Uterine Perforation	1	0.04%	0.03%
Salpingo oophorectomy for Torsion	1	0.04%	0.03%
Hysterotomy for pregnancy in non-communicating horn	1	0.04%	0.03%
<b>Other Surgeries</b>	<b>14</b>	<b>0.62%</b>	<b>0.44%</b>
Uterine Artery Embolization	1	0.04%	0.03%
Vaginal sutures (after 15 week surgical termination for ongoing pregnancy)	1	0.04%	0.03%
Paracenteses (multiple, same patient, death)	1	0.04%	0.03%
Necrotizing fasciitis debridement and below knee amputation	1	0.04%	0.03%
Upper and lower endoscopy for bright red bleeding	1	0.04%	0.03%
Unknown surgery for deep venous thrombosis	1	0.04%	0.03%
Angioplasty	1	0.04%	0.03%
Cholecystectomy	2	0.09%	0.06%
Appendectomy	1	0.04%	0.03%
Laceration repair (scalp, chin)	2	0.09%	0.06%
Unknown Surgery	2	0.09%	0.06%
<b>Total</b>	<b>2243</b>	<b>100%</b>	<b>70.16%</b>

**Table 2 – Treatment (Continued)**

<b>Location of Surgery</b>	<b>Location of Surgery (n)</b>	<b>Location of Surgery (%)</b>
<b>All Surgeries</b>	<b>2243</b>	<b>100.00%</b>
Hospital or ER	1291	57.56%
Outpatient	952	42.44%
<b>D&amp;C</b>	<b>2146</b>	<b>100.00%</b>
Hospital or ER	1194	55.64%
Outpatient	952	44.36%
<b>Surgical Provider for D&amp;C</b>	<b>Surgical Provider (n)</b>	<b>Surgical Provider (%)</b>
Hospital/ER	1194	55.64%
Abortion Provider	853	39.75%
Other Provider	99	4.61%
<b>Total</b>	<b>2146</b>	<b>100%</b>
<b>Indication for D&amp;Cs</b>	<b>Indication for D&amp;C (n)</b>	<b>Indication for D&amp;C (%)</b>
<b>Confirmed D&amp;C</b>	<b>2146</b>	<b>100%</b>
RPOC (confirmed by pathology or ultrasound)	897	41.80%
RPOC/Bleeding (no pathology provided)	1058	49.30%
Ongoing pregnancy, surgical termination by D&C	139	6.48%
RPOC ruled out	34	1.58%
Ectopic evaluation	12	0.56%
Molar pregnancy	2	0.09%
Not able to take misoprostol	4	0.19%
<b>Possible D&amp;C</b>	<b>680</b>	
Possible RPOC, unknown treatment, possible D&C	450	
RPOC confirmed by U/S but D&C not documented	29	
Ongoing pregnancy Unknown outcome, possible D&C	201	
<b>TOTAL (Confirmed and Possible)</b>	<b>2826</b>	

**Table 2 – Treatment (Continued)**

<b>Transfusions</b>	<b>Transfusions (n)</b>	<b>Transfusions (%)</b>	<b>Transfusion: % of (3197) Unique US AERs (%)</b>
<b>PRBC alone</b>	<b>365</b>	<b>75.88%</b>	<b>11.42%</b>
1U	32	6.65%	1.00%
1-2U	1	0.21%	0.03%
2U	246	51.14%	7.69%
2.5U	1	0.21%	0.03%
3U	45	9.36%	1.41%
4U	27	5.61%	0.84%
5U	5	1.04%	0.16%
6U	5	1.04%	0.16%
7U	2	0.42%	0.06%
10U	1	0.21%	0.03%
<b>Other Blood products</b>	<b>9</b>	<b>1.87%</b>	<b>0.28%</b>
1 U FFP	1	0.21%	0.03%
2 U PRBC/1 U FFP	1	0.21%	0.03%
2 U PRBC/ 4 U FFP	1	0.21%	0.03%
3 U PRBC/ 1 U FFP	1	0.21%	0.03%
4 U PRBC/ 1 U FFP	1	0.21%	0.03%
4 U PRBC/ 2 U FFP	1	0.21%	0.03%
5 U PRBC/ 4 U FFP	1	0.21%	0.03%
6 U PRBC/ 2 U FFP	1	0.21%	0.03%
7 U PRBC/ FFP and Platelets unknown amount	1	0.21%	0.03%
<b>Unknown amount (documented as given, units not recorded)</b>	<b>107</b>	<b>22.25%</b>	<b>3.35%</b>
<b>Total<sup>d</sup></b>	<b>481</b>	<b>100%</b>	<b>15.05%</b>

<sup>a</sup> Because of rounding, percentages may not appear to add up exactly.

<sup>b</sup> With or without suction, one with hysteroscopy.

<sup>c</sup> There were 8 patients who had 2 D&Cs and one who required uterine artery embolization. There were 4 perforations: two had resultant hysterectomies, one had a laparoscopy, and one received 2 U PRBCs but no documented surgery.

<sup>d</sup> Additionally there were 7 patients who likely received transfusion, but was not recorded, 3 patients who refused transfusion, and 1 patient for whom transfusion was considered but not given.



**Table 3 – Relationship of Misoprostol to Hemorrhage<sup>a</sup>**

	Mifepristone + Misoprostol		Mifepristone alone		Unknown		Mifepristone + Misoprostol + unknown <sup>b</sup>		Mifepristone alone + unknown <sup>c</sup>	
	n	%	n	%	n	%	n	%	n	%
<b>No Hemorrhage</b>	<b>1484</b>	<b>48.56%</b>	<b>45</b>	<b>77.59%</b>	<b>30</b>	<b>35.71%</b>	<b>1514</b>	<b>48.23%</b>	<b>75</b>	<b>52.82%</b>
<b>Hemorrhage</b>	<b>1572</b>	<b>51.44%</b>	<b>13</b>	<b>22.41%</b>	<b>54</b>	<b>64.29%</b>	<b>1625</b>	<b>51.77%</b>	<b>67</b>	<b>47.18%</b>
Death	1	0.03%	0	0.00%	0	0.00%	1	0.03%	0	0.00%
Life threatening	441	14.43%	5	8.62%	20	23.81%	461	14.69%	25	17.61%
Severe	633	20.71%	3	5.17%	6	7.14%	639	20.36%	9	6.34%
Moderate	101	3.30%	1	1.72%	4	4.76%	105	3.35%	5	3.52%
Uncodable	396	12.96%	4	6.90%	24	28.57%	420	13.38%	28	19.72%
<b>Total US AERs</b>	<b>3056</b>	<b>100%</b>	<b>58</b>	<b>100%</b>	<b>84</b>	<b>100%</b>	<b>3139</b>	<b>100%</b>	<b>142</b>	<b>100%</b>

<sup>a</sup> Because of rounding, percentages may not appear to add up exactly.

<sup>b</sup> Assumes all unknowns took both mifepristone and misoprostol.

<sup>c</sup> Assumes all unknowns took mifepristone, but not misoprostol.

## Discussion

This article is critically important considering the paucity of published literature on mifepristone safety and the minimal analysis done on the AERs by the FDA.

### *Ectopic Pregnancies*

Although reported as AEs, ectopic pregnancies are not a direct adverse event from the medication, but rather a contraindication to its administration. They were reported as adverse events because the ectopic pregnancies were missed.

The American College of Obstetricians and Gynecologists (ACOG) notes that “According to the Centers for Disease Control and Prevention, ectopic pregnancy accounts for approximately 2% of all reported pregnancies. However, the true current incidence of ectopic pregnancy is difficult to estimate because many patients are treated in an outpatient setting where events are not tracked, and national surveillance data on ectopic pregnancy have not been updated since 1992. Despite improvements in diagnosis and management, ruptured ectopic pregnancy continues to be a significant cause of pregnancy-related mortality and morbidity. In 2011–2013, ruptured ectopic pregnancy accounted for 2.7% of all pregnancy-related deaths and was the leading cause of hemorrhage-related mortality.”<sup>36</sup>

<sup>36</sup> ACOG Practice Bulletin No. 193: Tubal Ectopic Pregnancy, Obstet Gynecol: March 2018; 131(3): e91-e103.  
doi:10.1097/AOG.0000000000002560



Confirmed/suspected ectopic pregnancy and undiagnosed adnexal mass are contraindications to mifepristone use under current prescribing requirements. The label warnings state: "Ectopic pregnancy: exclude before treatment."<sup>37</sup> Unfortunately, it is difficult to rule out ectopic pregnancy by history alone because, "half of all women who receive a diagnosis of an ectopic pregnancy do not have any known risk factors."<sup>38</sup> According to ACOG Practice Bulletin No. 193, "The minimum diagnostic evaluation of a suspected ectopic pregnancy is a transvaginal ultrasound evaluation and confirmation of pregnancy." Of the 75 reported ectopic pregnancies in the FDA AERs we analyzed, over a third were known to be ruptured including one death. Clearly, an ultrasound should be required prior to the administration of mifepristone to document that the pregnancy is located within the uterus. Although not 100% effective, this will screen for ectopic pregnancy, confirm gestational age, which can be inaccurate based on menstrual history alone,<sup>39</sup> and screen for adnexal masses, another contraindication to mifepristone use.<sup>40</sup>

### ***Ongoing pregnancies***

Of the women with an ongoing pregnancy, less than a third were known to have proceeded with termination of the pregnancy, and almost a quarter were known to have kept their pregnancy; in almost half, the outcome was unknown. The significant percentage of women with ongoing pregnancy who changed their mind and chose to keep their pregnancy, after initially choosing termination, raises concerns regarding the pre-abortion counseling and informed consent they received. Women undergoing abortion should receive the same quality of informed consent and pre-procedural counseling that is standard of care prior to other medical treatment or surgery. It is imperative that women considering abortion be provided adequate and complete information and counseling on risks, advantages, disadvantages, and alternative options.

Additionally, the high percentage of women with ongoing pregnancies for whom there is no follow up or known outcome is concerning. As health care providers we are to continue to care for our patients and manage any complications, yet in the AERs we reviewed this was not typically the case for the abortion provider. Furthermore, a federal registry of known outcomes and birth defects is imperative. One of the initial FDA post-marketing requirements for

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<sup>37</sup> MIFEPREX. Package insert. Danco; 2016. Approved March 2016. p. 1. Accessed November 13, 2020. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2016/020687s020lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020687s020lbl.pdf)

<sup>38</sup> ACOG Practice Bulletin No. 193: Tubal Ectopic Pregnancy, Obstet Gynecol: March 2018; 131(3): e91-e103. doi: 10.1097/AOG.0000000000002560

<sup>39</sup> Shipp, Thomas D. 2020. Overview of ultrasound examination in obstetrics and gynecology. Lit Rev current through Dec 2020. UpToDate. Edited by Barss A Vanessa. Wolters Kluwer. June 10, 2020. Accessed January 11, 2021. [https://www.uptodate.com/contents/ectopic-pregnancy-clinical-manifestations-and-diagnosis/print?source=history\\_widget](https://www.uptodate.com/contents/ectopic-pregnancy-clinical-manifestations-and-diagnosis/print?source=history_widget).

<sup>40</sup> MIFEPREX. Package insert. Danco; 2016. Approved March 2016. Accessed November 13, 2020. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2016/020687s020lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020687s020lbl.pdf)

Danco was a surveillance study of outcomes of ongoing pregnancies.<sup>41</sup> The FDA released them from this post-marketing commitment in January 2008 because Danco reported that only one or two ongoing pregnancies per year were followed for final outcomes in part because of consent requirements.<sup>42</sup> This is disturbing in light of the percentage of women in our analysis who kept their pregnancies, as well as those with ongoing pregnancy and unknown outcomes, all of whom could have been followed for final outcomes. The significant lack of follow-up of ongoing pregnancies (44.47% with unknown outcomes) and the very minimal information on those who chose to keep the pregnancy, highlights the need for a national registry especially considering the teratogenicity of misoprostol.<sup>43</sup>

### ***Relationship of Misoprostol to Hemorrhage***

The Creinin study of abortion pill reversal was stopped for safety concerns due to hemorrhage in 3 of the 12 study participants.<sup>44</sup> One of the conclusions of that study was that “Patients who use mifepristone for a medical abortion should be advised that not using misoprostol could result in severe hemorrhage, even with progesterone treatment.”<sup>45</sup> The authors hypothesized that the absence of misoprostol caused these women to hemorrhage. The women who had documented use of misoprostol in our database hemorrhaged at a higher rate than those documented not to have taken misoprostol.

### ***Reporting of Adverse Events***

Although not the initial goal of this study, the analysis of the AERs revealed glaring deficiencies in the AE reporting system making it difficult to properly evaluate adverse events. When mifepristone was approved in 2000, FDA required that providers “must report any hospitalization, transfusion or other serious event to Danco Laboratories.”<sup>46</sup> This created an inherent conflict of interest as it is not in the best interest of the entities or providers to report adverse events to those regulating them. Because only severe events were reportable, this requirement likely resulted in an underestimation of moderate and mild AEs. It

<sup>41</sup> Center for Drug Evaluation and Research. NDA 20-687. Approval Letter for MIFEPREX (mifepristone) Tablets, 200 mg to Population Council. Food and Drug Administration. Written September 28, 2000. Accessed November 13, 2020. [https://www.accessdata.fda.gov/drugsatfda\\_docs/applletter/2000/20687appltr.htm](https://www.accessdata.fda.gov/drugsatfda_docs/applletter/2000/20687appltr.htm)

<sup>42</sup> 2016 03 20 FDA resp to Cit Pet.pdf. Docket No. FDA-2002-P-0364. FDA. March 29, 2016. p. 31. Accessed November 13, 2020.

<https://aaplog.wildapricot.org/resources/2016%2003%2020%20%20FDA%20resp%20to%20Cit%20Pet.pdf>

<sup>43</sup> Cytotec (misoprostol tablets). Package insert. G.D. Searle; Revised November 2012. Accessed November 13, 2020. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2012/019268s047lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/019268s047lbl.pdf)

<sup>44</sup> Creinin MD, Hou MY, Dalton L, Steward R, Chen MJ. Mifepristone Antagonization With Progesterone to Prevent Medical Abortion: A Randomized Controlled Trial. *Obstet Gynecol.* 2020;135(1):158-165. doi:10.1097/AOG.0000000000003620

<sup>45</sup> Creinin MD, Hou MY, Dalton L, Steward R, Chen MJ. Mifepristone Antagonization With Progesterone to Prevent Medical Abortion: A Randomized Controlled Trial. *Obstet Gynecol.* 2020;135(1):5. doi:10.1097/AOG.0000000000003620

<sup>46</sup> M I F E P R E X™(Mifepristone) Tablets, 200 mg Prescriber’s agreement. Food and Drug Administration. September 28, 2000, 1-2. Accessed November 16, 2020. <http://wayback.archive-it.org/7993/20170113112742/http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111364.pdf>

is also likely that some of the AEs that we coded as Mild or Moderate were actually Severe but there was not enough information in the AER for us to justify coding them as Severe. In March 2016, the FDA substantially reduced the prescribing requirements and changed the drug protocol<sup>47</sup> and yet at the same time eliminated reporting requirements except for deaths.<sup>48</sup> With the relaxation of reporting requirements, the ability to perform any relevant post-marketing evaluation of mifepristone was lost. It is imperative for the safety of women that the FDA restore and strengthen the 2011 REMS requirements.

The information in the AERs is almost exclusively obtained from abortion providers, rather than the physician treating the complication, yet in this analysis, abortion providers managed only 39.75% of surgical complications (a number which is likely much lower since these are only the cases which are known to the abortion provider). Throughout the reports, there was also a lack of detail and many patients who were simply “lost to follow-up.” This resulted in 16.80% of the AERs being Uncodable as to severity and likely under-coding of many AERs and AEs, as coding could only be assigned based on the scant information provided. Many of the AEs experienced by women were unknown to the abortion provider until the follow-up examination, which is troubling considering the poor follow-up rate and elimination of the requirement for an in-office follow up visit. Some of the patient deaths were not known to the abortion provider until they saw the death in an obituary or were contacted by an outside source. Because of this, in addition to abortion providers, hospitals, emergency departments, and private practitioners should be required to report AEs.

Complications occur in the best of hands in all areas of medicine, but as physicians, we are responsible to manage those complications and follow our patients through to resolution. The findings that: 1. the most common outcome of ongoing pregnancy was unknown outcome, 2. abortion providers performed less than half the D&Cs done for complications, and 3. a third of ectopic pregnancies (missed prior to administering the abortifacient) had unknown rupture status, leave us deeply concerned regarding the care these women received. A post-marketing requirement was that there be a “cohort-based study of safety outcomes of patients having medical abortion under the care of physicians with surgical intervention skills compared to physicians who refer their patients for surgical intervention.”<sup>49</sup> The applicant was released from this requirement because they stated that because there were so few providers

<sup>47</sup> GAO-18-292 Revised Mifeprex Labeling: Food and Drug Administration Information on Mifeprex Labeling Changes and Ongoing Monitoring Efforts. Report to Congressional Requesters. Food and Drug Administration. 2018. p. 7. Published March 2018. Accessed November 13, 2020. <https://www.gao.gov/assets/700/690914.pdf>

<sup>48</sup> NDA 20-687 MIFEPREX (mifepristone) Tablets, 200 mg: Risk Evaluation and Mitigation Strategy (REMS). Food and Drug Administration. 2016. p. 3, 6. Reference ID: 3909592. Published March 29, 2016. Accessed November 13, 2020. [https://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2016/020687Orig1s020RemsR.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/020687Orig1s020RemsR.pdf)

<sup>49</sup> Center for Drug Evaluation and Research. NDA 20-687. Approval Letter for MIFEPREX (mifepristone) Tablets, 200 mg to Population Council. Food and Drug Administration. Written September 28, 2000. Accessed November 13, 2020. [https://www.accessdata.fda.gov/drugsatfda\\_docs/appltr/2000/20687appltr.htm](https://www.accessdata.fda.gov/drugsatfda_docs/appltr/2000/20687appltr.htm)

without surgical intervention skills, no meaningful study could be done.<sup>50</sup> Yet, that same year the FDA changed the provider agreement to allow non-physicians to become prescribers.<sup>51</sup> These findings highlight the importance of follow-up and management of complications by the abortion provider. Allowing any further relaxation of mifepristone prescribing requirements will put women at an even higher risk of adverse events

### ***Limitations and Strengths***

It was not possible to calculate complication rates for mifepristone and misoprostol abortions based on AER data because there is no denominator for how many mifepristone abortions are performed in the U.S. since reporting is often voluntary and sporadic. For clarity, we specified the denominators we used.

Our analysis was limited by the fact that the number of AEs for which we received reports is likely a gross underestimation of the actual number of AEs that occurred. In our analysis, the surgical management of over half the complications was performed by someone other than the abortion provider, yet treating physicians are not required to report complications. Few reports were generated by those in Emergency Departments and hospitals who treated the complications.

Our analysis was also limited by the lack of information in the AERs, including redaction of critical dates, a paucity of diagnosis and treatment information, and lack of follow up.

Our study has several strengths. Our data comes from information provided to the FDA and is the largest analysis of AERs for mifepristone abortions. This data is publicly available under the Freedom of Information Act so that anyone can verify the data for themselves. This analysis reviews all AERs not reported in the first study by Gary.<sup>52</sup> Although heavily redacted, there was sufficient information in over 80% of the AERs to evaluate severity. An objective standardized system, CTCAEv3, was used to code for severity, and each AER was coded by at least two board-certified obstetrician-gynecologists or family medicine physicians.

### **Conclusions and Relevance**

This article is important because it augments the scant published literature on mifepristone safety.

Due to the lack of adequate reporting of adverse events, especially by those treating them, these unique AERs represent a fraction of the actual adverse events occurring in American women.

<sup>50</sup> 2016 03 20 FDA resp to Cit Pet.pdf. Docket No. FDA-2002-P-0364. FDA. March 29, 2016. p. 31. Accessed November 13, 2020.

<https://aaplog.wildapricot.org/resources/2016%2003%2020%20FDA%20resp%20to%20Cit%20Pet.pdf>

<sup>51</sup> GAO-18-292 Revised Mifeprex Labeling: Food and Drug Administration Information on Mifeprex Labeling Changes and Ongoing Monitoring Efforts. Report to Congressional Requesters. Food and Drug Administration. 2018. p. 7. Published March 2018. Accessed November 13, 2020. <https://www.gao.gov/assets/700/690914.pdf>

<sup>52</sup> Gary M, Harrison D. Analysis of Severe Adverse Events Related to the Use of Mifepristone as an Abortifacient. *Ann Pharmacother*. 2006 Feb 40(2):191-7. <https://doi.org/10.1345/aph.1G481>

Significant morbidity and mortality have occurred with the use of mifepristone as an abortifacient, including at least 24 US deaths reported by the FDA from September 2000 to December 2018. Because of this and the significant morbidity associated with this drug, the FDA should consider at a minimum reinstating the original 2011 REMS and strengthening the reporting requirements. The reporting of transfusions, hospitalizations, and other serious adverse events are essential.

Given the morbidity and mortality of undiagnosed ectopic pregnancy, a clear contraindication to the use of mifepristone, an ultrasound to confirm pregnancy location is essential before mifepristone is dispensed.

Considering the significant percentage of women with ongoing pregnancies who chose to continue their pregnancy, there must be reasonable waiting periods, parental involvement, and adequate pre-abortion counseling on all pregnancy options. It is also critical that a pregnancy registry be established.

In our analysis, the patients who used mifepristone alone had a lower rate of hemorrhage than those using mifepristone followed by misoprostol.

The FDA Adverse Event Reporting System is woefully inadequate to determine the post-marketing safety of mifepristone due to its inability to adequately assess the frequency or severity of adverse events. The reliance solely on interested parties to report, the large percentage of uncodable events, the redaction of critical clinical information unrelated to personally identifiable information, and the inadequacy of the reports highlight the need to overhaul the current AER System.

This analysis evaluated 3197 adverse events resulting from the use of mifepristone as an abortifacient and brought to light serious concerns about the safety requirements and care of women undergoing mifepristone abortion. Although complications may occur in the best of hands, and no medical procedure is without risks, safety measures must be employed to minimize these adverse outcomes. Women undergoing abortion should receive the same quality of informed consent and pre-procedural counseling that is standard of care prior to other medical treatment or surgery. It is imperative that women considering abortion be provided adequate and complete information and counseling on risks, advantages, disadvantages, and alternative options. Although there may be disagreements about the ethics of abortion, there must be total agreement that our patients—whether undergoing a medical abortion or otherwise—deserve the highest standard of medical care.

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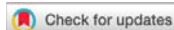
Authors would also like to acknowledge William Marshall of Judicial Watch for assistance with FOIA requests to the FDA.

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# Exhibit 46

Christina A. Cirucci, et al., *Mifepristone Adverse Events Identified by Planned Parenthood in 2009 and 2010 Compared to Those in the FDA Adverse Event Reporting System and Those Obtained Through the Freedom of Information Act*, 8 Health Servs. Rsch. & Managerial Epidemiology 1 (2021)



# Mifepristone Adverse Events Identified by Planned Parenthood in 2009 and 2010 Compared to Those in the FDA Adverse Event Reporting System and Those Obtained Through the Freedom of Information Act

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## Abstract

**Background:** As part of the accelerated approval of mifepristone as an abortifacient in 2000, the Food and Drug Administration (FDA) required prescribers to report all serious adverse events (AEs) to the manufacturer who was required to report them to the FDA. This information is included in the FDA Adverse Event Reporting System (FAERS) and is available to the public online. The actual Adverse Event Reports (AERs) can be obtained through the Freedom of Information Act (FOIA).

**Methods:** We compared the number of specific AEs and total AERs for mifepristone abortions from January 1, 2009 to December 31, 2010 from 1. Planned Parenthood abortion data published by Cleland et al. 2. FAERS online dashboard, and 3. AERs provided through FOIA and analyzed by Aultman et al.

**Results:** Cleland identified 1530 Planned Parenthood mifepristone cases with specific AEs for 2009 and 2010. For this period, FAERS online dashboard includes a total (from all providers) of only 664, and the FDA released only 330 AERs through FOIA. Cleland identified 1158 ongoing pregnancies in 2009 and 2010. FAERS dashboard contains only 95, and only 39 were released via FOIA.

**Conclusions:** There are significant discrepancies in the total number of AERs and specific AEs for 2009 and 2010 mifepristone abortions reported in 1. Cleland's documentation of Planned Parenthood AEs, 2. FAERS dashboard, and 3. AERs provided through FOIA. These discrepancies render the FAERS inadequate to evaluate the safety of mifepristone abortions.

## Keywords

mifepristone, misoprostol, adverse drug reaction reporting systems, drug-related side effects and adverse reactions, postmarketing product surveillance, induced abortion, steroidal abortifacient agents, United States food and drug administration

## Introduction

The accelerated approval of mifepristone in the United States (US) in 2000 included post-marketing restrictions to monitor safety. Prescribers were required to report any ongoing pregnancies, hospitalizations, transfusions, and other serious events to the manufacturer, who was required to submit them to the Food and Drug Administration (FDA).<sup>1</sup> Adverse events (AEs) are documented in the FDA Adverse Event Reporting System (FAERS), available online.<sup>2</sup> Copies of the actual Adverse Event Reports (AERs) can be obtained via the Freedom of Information Act (FOIA).<sup>3</sup>

A paper published by Cleland et al. analyzed eight adverse events/outcomes (AEs) from mifepristone abortions at 63

days and less performed by Planned Parenthood in 2009 and 2010. They analyzed hospital admissions, blood transfusions, emergency department (ED) treatments, intravenous (IV)

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antibiotics, infections requiring IV antibiotics or hospitalization, deaths, ongoing pregnancies, and ectopic pregnancies. Cleland explained that Planned Parenthood reports all significant AEs to Danco Laboratories, which submits them to the FDA, per the mifepristone prescribing information. Their analysis for these specific AEs led them to conclude that, “Among the 233 805 medical abortions provided at Planned Parenthood health centers in 2009 and 2010, significant adverse events or outcomes were reported in 1530 (0.65%) cases.”<sup>4</sup> Unless associated with another AE, they did not include data on incomplete abortion managed at Planned Parenthood or hemorrhage without transfusion, two of the most common AEs resulting from mifepristone abortion. They also admit that “we cannot exclude the possibility that some clinically significant adverse events or outcomes were not included. Some patients may have experienced a significant adverse event or outcome but did not follow up after their medical abortion.”<sup>4</sup> Cleland did not provide the loss to follow-up rate.

In 2021, Aultman et al. published an analysis of the AERs for mifepristone abortion from September 2000 to February 2019 (excluding those published by Gary in 2006) utilizing AERs obtained through FOIA.<sup>5,6</sup>

The objective of this paper was to compare the total number of AERs/cases (which may include more than one AE) and the individual AEs identified by Cleland for 2009 and 2010 mifepristone abortions from three sources: those identified by Planned Parenthood as published by Cleland, those currently posted on the FAERS dashboard, and those provided by the FDA in response to FOIA and analyzed by Aultman.

## Methods

We searched the FAERS dashboard for any US AERs related to mifepristone abortion occurring from January 1, 2009 through December 31, 2010 and tabulated the total number of AERs, hospital admissions, deaths, ongoing pregnancies, and ectopic pregnancies. The FAERS did not have enough information to evaluate for transfusion, ED visits, IV antibiotics, or infections requiring IV antibiotics or hospital admission. Since FAERS does not provide the “abortion date,” we used the “event date”; in cases where there was no “event date,” we used the “latest manufacturer received date.” We evaluated Aultman’s

AERs for the events in Cleland and confirmed any missing reports by searching the 6158 pages of AERs related to mifepristone abortion obtained by FOIA. In analyzing FOIA data, Aultman accounted for duplicates. In the FAERS data, we accounted for duplicates for deaths and ectopic pregnancies, but FAERS did not provide sufficient detail to do so for hospital admissions and ongoing pregnancies. We then compared the total number of reports, as well as hospitalizations, ongoing pregnancies, ectopic pregnancies, and deaths from Cleland, FAERS, and FOIA AERs for 2009 and 2010. Adverse events not reported by Cleland were not evaluated. The FAERS and FOIA total AERs include reports from all sources, not just from Planned Parenthood, and include all reports for those years, not just those with the eight AEs evaluated by Cleland.

## Results

Our analysis shows significant discrepancies between the number of AERs identified by Planned Parenthood as reported in Cleland, the number in the FAERS database, and the number received under FOIA. There are also discrepancies in the number of hospitalizations, ectopic pregnancies, and ongoing pregnancies.

### Total Reports (Figure 1)

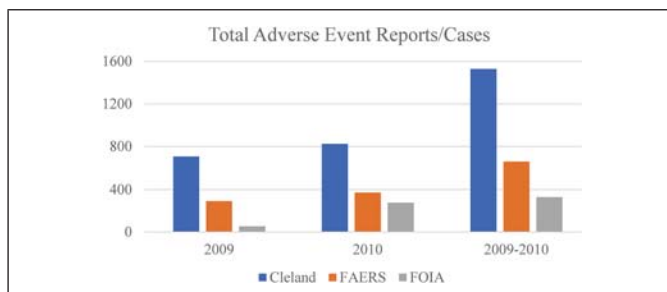
Cleland identified 1530 cases involving eight specific AEs after Planned Parenthood mifepristone abortion in 2009 and 2010. The FAERS dashboard contains only 664 AERs for this period, and only 330 were provided through FOIA. Both include AERS with other types of adverse events not included by Cleland and include reports from all sources, not just Planned Parenthood.

### Specific Adverse Events/Outcomes (Table 1)

Cleland identified 548 ongoing pregnancies after mifepristone abortion in 2009, the FAERS dashboard includes just 56, and only seven were received via FOIA. For 2010, Cleland identified 610 ongoing pregnancies, FAERS contains just 39, and only 32 were obtained via FOIA. Cleland identified 70 hospital admissions in 2009 and 65 in 2010. FAERS includes 87 and 125, respectively, but the FDA only provided 14 and 94 via FOIA. Ectopic pregnancy, although not caused by mifepristone, is a contraindication to its use. Cleland reported eight ectopic pregnancies in 2009 and eight in 2010. FAERS includes eight for 2009 and nine for 2010. The FOIA AERs have only one ectopic for 2009 and eight for 2010. Cleland reported no deaths in 2009 and one in 2010. FAERS and FOIA were consistent with one death in 2009 and two in 2010.

## Discussion

The total number of AEs published in Cleland is significantly higher than the number in the FAERS database, even though Cleland did not evaluate all AEs, including



**Figure 1.** Comparison of total adverse event reports from three sources.

**Table 1.** Comparison of Number of Specific Adverse Events<sup>a</sup> from Three Sources.

	2009			2010			Total 2009 to 2010		
	Cleland	FAERS <sup>b</sup>	FOIA	Cleland	FAERS <sup>b</sup>	FOIA	Cleland	FAERS <sup>b</sup>	FOIA
<b>Hospital Admission</b>	70	87	14	65	125	94	135	212	108
<b>Transfusion</b>	42		10	72		59	114		69
<b>ED Treatment</b>	87		27	151		105	238		132
<b>IV Antibiotics</b>	23		5	34		27	57		32
<b>Infection requiring IV Antibiotics or Admission</b>	14		4	23		21	37		25
<b>Death</b>	0	1	1	1	2	2	1	3	3
<b>Ongoing Pregnancy</b>	548	56	7	610	39	32	1158	95	39
<b>Ectopic Pregnancy</b>	8	8	1	8	9	8	16	17	9

<sup>a</sup>Events are not mutually exclusive.<sup>b</sup>If blank, FAERS dashboard does not provide this detail.

failed abortions treated at Planned Parenthood.<sup>4</sup> The discrepancy is particularly concerning because the total number of AEs and AERs in the FAERS should be significantly higher than Cleland since Planned Parenthood performs only 37% of US abortions.<sup>7</sup> It is unclear why so many cases identified by Planned Parenthood in Cleland do not appear in FAERS. Cleland states, “In accordance with the mifepristone prescribing information, Planned Parenthood Federation of America reports all significant adverse events and outcomes to Danco Laboratories, the US distributor of mifepristone, which in turn reports them to the FDA.”<sup>4</sup> If this claim is true, then either Danco did not report a significant number of adverse events to the FDA, or the FDA did not include them in FAERS. It also raises the question of whether FAERS includes all complications reported by the other 63% of abortion providers.

We are concerned that FDA and others will continue to rely on Cleland’s statement, “significant adverse events or outcomes were reported in 1530 (0.65%) cases”<sup>4</sup> to claim that the complication rate for the abortion pill regimen is low. Although Cleland’s paper is a study of over 200 000 abortions and is cited extensively in support of the safety of medical abortion<sup>8–11</sup> the analysis excludes the most common adverse events (retained products of conception and hemorrhage not requiring transfusion). Additionally, Cleland’s reported complication rate of 0.65% is only a report of the complications known to Planned Parenthood. Cleland does not report the percent of patients lost to follow-up.<sup>4</sup>

There is also concern that the FDA will continue to rely on the FAERS to make decisions about removing mifepristone REMS, despite the findings herein that FAERS does not include all the events even known to the abortion provider. To compound this problem, in 2016, the FDA eliminated the requirement to report adverse events resulting from mifepristone other than death.<sup>12</sup> Nevertheless, in her April 12, 2021 letter to the American College of Obstetricians and Gynecologists, FDA Commissioner Janet Woodcock stated

that, based on a review of post-marketing AEs from January 27, 2020, to January 12, 2021, the in-person dispensing requirements in the mifepristone REMS would not be enforced.<sup>13</sup> It is alarming that policy decisions that affect women’s safety are based on a lack of information in the FAERS. Whether the inaccuracy of FAERS extends to required reporting for other medications is unknown to us, but the findings in this paper have significant implications for drug safety evaluation in general.

The ability of the FAERS to accurately identify complications from mifepristone abortion depends on 1. the abortion provider being aware of the adverse event, 2. the provider reporting the adverse event to the manufacturer, 3. the manufacturer reporting to the FDA, and 4. the FDA including the event in the FAERS. One problem inherent in this system is that adverse events unknown to the abortion provider or occurring in patients lost to follow-up will be missed. In addition, ED physicians or treating physicians other than the abortion provider were never obligated to report and may not even be aware of the system. For those events known to Planned Parenthood, it is unclear whether the error occurred in the abortion provider reporting to the manufacturer, the manufacturer reporting to the FDA, or the FDA uploading to the database.

FDA compliance in response to FOIA requests is required by law.<sup>3</sup> The number of AERs supplied under FOIA is much lower than the number in the FAERS database and known to the FDA at the time. Although there may be extenuating circumstances requiring that some information be withheld, withholding information, especially to this extent, interferes with independent, scientific analysis necessary to validate claims of safety and efficacy.

### Strengths and Limitations

One of the limitations of this study is that Cleland only reported on a limited number of possible AEs. Because of the scant information included in the FAERS, we could not even compare all AEs reported by Cleland. Since we do not have

access to the Planned Parenthood records, reports cannot be evaluated on a patient-by-patient basis but only as a composite.

One of the strengths of this study is that it is the first known study comparing FAERS data with an outside report of mifepristone complications.

## Conclusions

There are significant discrepancies in the number of AEs and total AERs reported for 2009 and 2010 mifepristone abortions identified by Planned Parenthood as reported by Cleland, those in FAERS, and those provided by FOIA, impugning the reliability of FAERS to evaluate the safety or efficacy of mifepristone abortions at a time when the FDA is under pressure to eliminate REMS on mifepristone.<sup>14,15</sup> The FDA used their review of post-marketing adverse events that occurred in 2020 and 2021 as a rationale for removing the in-person dispensing requirements for mifepristone during COVID, even though reporting requirements (other than death) were eliminated in 2016.<sup>13</sup> Whether Planned Parenthood did not submit all the AEs to Danco, Danco did not submit all to the FDA, or the FDA did not include all is unknown. By withholding a significant number of AERs, the FDA did not adequately comply with the FOIA request by the authors of the Aultman paper, hampering their ability to analyze the data. These discrepancies, and the fact that since 2016, reporting AEs other than deaths is no longer required,<sup>12</sup> demonstrate that the FAERS is inadequate to evaluate the safety of mifepristone.

## Declaration of Conflicting Interests


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## References

- Center for Drug Evaluation and Research. NDA 20-687. Approval Letter for MIFEPREX (mifepristone) Tablets, 200 mg to Population Council. Food and Drug Administration. Written September 28, 2000. Accessed November 18, 2021. [https://www.accessdata.fda.gov/drugsatfda\\_docs/appltr/2000/20687appltr.htm](https://www.accessdata.fda.gov/drugsatfda_docs/appltr/2000/20687appltr.htm)
- FDA Adverse Event Reporting System (FAERS) Public Dashboard. FDA. Updated October 22, 2021. Accessed November 11, 2021. <https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-public-dashboard>
- What is FOIA? US Dept of Justice. FOIA. Accessed November 16, 2021. <https://www.foia.gov/about.html>
- Cleland K, Creinin MD, Nucatola D, Nshom M, Trussell J. Significant adverse events and outcomes after medical abortion. *Obstet Gynecol.* 2013;121(1):166-171. <https://doi.org/10.1097/aog.0b013e3182755763>
- Aultman K, Cirucci C, Harrison D, et al. Deaths and severe adverse events after the Use of mifepristone as an abortifacient from September 2000 to February 2019. *Issues Law Med.* 2021;36(1):326. <https://issuesinlawandmedicine.com/wp-content/uploads/2021/01/Deaths-and-Severe-Adverse-Events-after-the-use-of-Mifepristone-as-an-Abortifacient-from-September-2000-to-February-2019-copy5.pdf>
- Gary MM, Harrison DJ. Analysis of severe adverse events related to the Use of mifepristone as an abortifacient. *Ann Pharmacother.* 2006;40(2):191-197. <https://doi.org/10.1345/aph.1G481>
- Communities Need Clinics: The Essential Role of Independent Abortion Clinics in the United States. Abortion Care Network. 2020;2. Accessed November 15, 2021. <https://abortioncarenetwork.org/wp-content/uploads/2020/12/CommunitiesNeedClinics-2020.pdf>
- National Academies of Sciences, Engineering, and Medicine. *The Safety and Quality of Abortion Care in the United States*. The National Academies Press; 2018: Kindle Locations 1351–1367. Accessed 11–29–21. <https://doi.org/10.17226/24950>
- Gill R, Norman WV. Telemedicine and medical abortion: dispelling safety myths, with facts. *Mhealth.* 2018;4(3):1–4. <https://doi.org/10.21037/mhealth.2018.01.01>
- Upadhyay UD, Schroeder R, Roberts SCM. Adoption of no-test and telehealth medication abortion care among independent abortion providers in response to COVID-19. *Contracept X.* 2020;2-(100049):1–5. <https://doi.org/10.1016/j.conx.2020.100049>
- Gatter M, Cleland K, Nucatola DL. Efficacy and safety of medical abortion using mifepristone and buccal misoprostol through 63 days. *Contraception.* 2015;91(4):269-273. <https://doi.org/10.1016/j.contraception.2015.01.005>
- Food and Drug Administration. *Information on Mifeprex Labeling Changes and Ongoing Monitoring Efforts*. GAO-18-292 Report to Congressional Requesters. March 2018;8. Accessed November 30, 2021. <https://www.gao.gov/assets/700/690914.pdf>
- Letter from Woodcock J. (Acting Commissioner of Food and Drugs) to Phipps MG (Chief Executive Officer ACOG) and Grobman, W (Pres Society for Fetal-Maternal Medicine). ACLU. April 12, 2021. p. 2. Accessed November 15, 2021. [https://www.aclu.org/sites/default/files/field\\_document/fda\\_acting\\_commissioner\\_letter\\_to\\_acog\\_april\\_12\\_2021.pdf](https://www.aclu.org/sites/default/files/field_document/fda_acting_commissioner_letter_to_acog_april_12_2021.pdf)
- Letter to Joseph R. Biden (President of the US) from the ACLU and others. Planned Parenthood. March 18, 2021. 1-5. Accessed November 30, 2021. [https://www.plannedparenthood.org/uploads/filer\\_public/28/b2/28b21706-7f25-4cd6-b43b-ee340a6681d7/coalition\\_letter\\_to\\_biden\\_administration\\_re\\_mifepristone\\_3\\_18\\_21\\_final.pdf](https://www.plannedparenthood.org/uploads/filer_public/28/b2/28b21706-7f25-4cd6-b43b-ee340a6681d7/coalition_letter_to_biden_administration_re_mifepristone_3_18_21_final.pdf)
- Chelius v. Becerra, Case 1:17-cv-00493-JAO-RT. Document 148. P. 3191. (DC Hawaii) July 9, 2021. Accessed November 30, 2021. [https://www.aclu.org/sites/default/files/field\\_document/chelius\\_v.\\_becerra\\_-\\_joint\\_motion\\_for\\_stay\\_pending\\_agency\\_review\\_may\\_7\\_2021.pdf](https://www.aclu.org/sites/default/files/field_document/chelius_v._becerra_-_joint_motion_for_stay_pending_agency_review_may_7_2021.pdf)



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# Exhibit 47

FDA, *FDA Adverse Event Reporting System (FAERS)*  
*Electronic Submissions*

# FDA Adverse Event Reporting System (FAERS) Electronic Submissions

## Updates for Electronic Submission of Individual Case Safety Reports (ICSRs) to FAERS

FDA recently updated the following guidances for industry to incorporate technical updates: [E2B \(R3\) Electronic Transmission of Individual Case Safety Reports Implementation Guide – Data Elements and Message Specification \(/regulatory-information/search-fda-guidance-documents/e2br3-electronic-transmission-individual-case-safety-reports-implementation-guide-data-elements-and\)](#) and [Appendix to the Implementation Guide – Backwards and Forwards Compatibility \(/regulatory-information/search-fda-guidance-documents/e2br3-electronic-transmission-individual-case-safety-reports-implementation-guide-appendix\)](#).

## Premarketing Safety Reporting

In preparation for the electronic transmission of premarketing safety reports in the International Council for Harmonisation (ICH) E2B(R3) format, FDA has posted the following documents regarding the electronic submission of ICSRs for certain investigational new drug application (IND) safety reports for drug and biological products and IND-exempt bioavailability/bioequivalence (BA/BE) safety reports to FAERS. These documents are posted to help sponsors prepare their systems for electronic submission of IND safety reports in the E2B(R3) format.

1. [Providing Regulatory Submissions in Electronic Format: IND Safety Reports - Draft Guidance for Industry](https://www.fda.gov/regulatory-information/search-fda-guidance-documents/providing-regulatory-submissions-electronic-format-ind-safety-reports-guidance-industry) (<https://www.fda.gov/regulatory-information/search-fda-guidance-documents/providing-regulatory-submissions-electronic-format-ind-safety-reports-guidance-industry>) (October 2019)
2. [Electronic Submission of IND Safety Reports - Technical Conformance Guide](https://www.fda.gov/regulatory-information/search-fda-guidance-documents/electronic-submission-ind-safety-reports-technical-conformance-guide) (<https://www.fda.gov/regulatory-information/search-fda-guidance-documents/electronic-submission-ind-safety-reports-technical-conformance-guide>) (April 2022)
3. [Technical Specifications Document - FDA Regional Implementation Guide for E2B\(R3\) Electronic Transmission of Individual Case Safety Reports for Drug and Biological Products](https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fda-regional-implementation-guide-e2br3-electronic-transmission-individual-case-safety-reports-drug) (<https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fda-regional-implementation-guide-e2br3-electronic-transmission-individual-case-safety-reports-drug>) (August 2022)
4. [Electronic Submission of Expedited Safety Reports From IND-Exempt BA/BE Studies - Draft Guidance for Industry](https://www.fda.gov/regulatory-information/search-fda-guidance-documents/electronic-submission-expedited-safety-reports-ind-exempt-ba-be-studies-draft-guidance-industry) ([https://www.fda.gov/regulatory-information/search-fda-guidance-](https://www.fda.gov/regulatory-information/search-fda-guidance-documents/electronic-submission-expedited-safety-reports-ind-exempt-ba-be-studies-draft-guidance-industry)

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[documents/electronic-submission-expedited-safety-reports-ind-exempt-babe-studies-guidance-industry](#)). (August 2022)

5. [FDA E2B\(R3\) Core and Regional Data Elements and Business Rules \(/media/157982/download\)](#) (Excel file August 2022)
6. [FDA ICSR XML Instances \(/media/157983/download\)](#) (zip file August 2022)

Please note, FDA is not currently accepting the submission of premarket ICSRs in the E2B(R3) format. Please continue to submit IND safety reports using eCTD format and IND-exempt BA/BE safety reports on Form FDA 3500A. FDA will update this web page when final guidance for IND safety reporting is published, and when FDA will accept IND and IND-exempt BA/BE safety reports in E2B(R3) format on a voluntary basis. FDA will also update this web page to communicate when submission of safety reports in E2B(R3) format is required for certain INDs after the period of voluntary submission.

## Postmarketing Safety Reporting

In preparation for the receipt of postmarketing safety reports in the E2B(R3) format, FDA has posted the following documents regarding the electronic submission of safety reports for drug and biological products to FAERS. These documents are posted to help prepare systems for electronic submissions of postmarketing safety reports.

1. [Technical Specifications Document - FDA Regional Implementation Guide for E2B\(R3\) Electronic Transmission of Individual Case Safety Reports for Drug and Biological Products \(https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fda-regional-implementation-guide-e2br3-electronic-transmission-individual-case-safety-reports-drug\)](#) (August 2022)
2. [FDA E2B\(R3\) Core and Regional Data Elements and Business Rules \(/media/157982/download\)](#) (Excel file August 2022)
3. [FDA E2B\(R3\) Forward Compatible Rules \(https://www.fda.gov/media/157993/download\)](#) (Excel file April 2022)
4. [FDA ICSR XML Instances \(/media/157983/download\)](#) (zip file August 2022)
5. [Providing Submissions in Electronic Format – Postmarketing Safety Reports: Guidance for Industry \(https://www.fda.gov/regulatory-information/search-fda-guidance-documents/providing-submissions-electronic-format-postmarketing-safety-reports\)](#) (April 2022)

Please note, FDA is not currently accepting the submission of postmarketing ICSRs in the E2B(R3) format. FDA will update this web page when postmarketing ICSRs will be accepted in the E2B(R3) format. In the meantime, please continue to submit postmarketing ICSRs in the E2B(R2) format.

For questions related to this update, please contact the FAERS electronic submission coordinator at [faersesub@fda.hhs.gov](mailto:faersesub@fda.hhs.gov) (<mailto:faersesub@fda.hhs.gov>).

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This page provides drug and nonvaccine biological product manufacturers, distributors, packers, outsourcing facilities, and other interested parties with information about FDA Adverse Event Reporting System (FAERS) electronic submissions and instructions on how to electronically submit postmarketing individual case safety reports (ICSRs) with and without attachments.

Since 2000, FDA has accepted electronic submissions of both expedited and non-expedited Individual Case Safety Reports (ICSRs) for human drug and nonvaccine biologic products. To date, FDA has only accepted electronic submissions of ICSR in the XML format, prepared in accordance with International Conference on Harmonisation-E2B (ICH E2B). (</media/76278/download>) (PDF - 266KB) to transmit information directly from database-to-database using standardized (ICH E2B(M)) data elements.

Starting June 10, 2015,\* FDA is requiring that applicants electronically submit all ICSR, ICSR attachments, and periodic safety reports. There are two options for submitting ICSR electronically:

- Database-to-database transmission ( "E2B")
- The Safety Reporting Portal (SRP) by manually entering the data via our SRP portal.
- Attachments: for both methods, we will only accept attachments in the PDF format.

*\*FDA issued a final rule on June 10, 2014, that requires industry to submit post-marketing safety reports in an electronic format. See the rule at: FDA issues final rule on postmarketing safety report in electronic format (<http://wayback.archive-it.org/7993/20170111002213/http://www.fda.gov/Drugs/DrugSafety/ucm400526.htm>) ↗ (<http://www.fda.gov/about-fda/website-policies/website-disclaimer>) (FDA Archive).*

Submitting Individual Case Safety Reports (ICSRs), ICSR Attachments, & Periodic Safety Reports (PSRs)

## 1. Electronic submission of ICSR

You have the 2 options for submitting ICSR electronically.

### ICSR Option A: Database-to-Database Transmission ("E2B")

- ICSR must be submitted in the XML format.
- Attachments must be in the pdf format.
- See document "Specifications for Preparing and Submitting Electronic ICSR and ICSR Attachments (</media/132096/download>)" (PDF - 204KB). XML files are submitted to the FDA via the Electronic Submissions Gateway (ESG).
- For additional instruction on how to begin submitting ICSR in the XML format, go to our document titled, "Steps to Submitting ICSR Electronically in the XML

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Format." (</drugs/fda-adverse-event-reporting-system-faers/steps-submitting-e2br2-icsrs-electronically-xml-format>).

## ICSR Option B: Safety Reporting Portal (SRP)

Applicants and non-applicants who do not have database-to-database capability may submit electronic ICSRs using the SRP. To submit via SRP, you must have an account to access the portal site. Those who are Gateway partners cannot use the SRP. Gateway partners are those companies that submit electronically via the Electronic Submission Gateway.

### Steps for requesting an SRP account

- Contact [FAERSESUB@fda.hhs.gov](mailto:FAERSESUB@fda.hhs.gov) (<mailto:FAERSESUB@fda.hhs.gov>) to advise FDA of your intent to begin submitting via the SRP.

### SRP account activation

- Your account will be activated in about 7 to 10 business days.
- You will be notified via email with the subject line "SRP Account Activation" that will include the web link to the SRP portal along with account information.
- After receiving this email, your account will be considered active and you may begin submitting reports.

## 2. Submitting ICSR Attachments

Attachments to ICSRs include supporting information for ICSRs such as relevant hospital discharge summaries and autopsy reports, death certificate, and published articles for ICSRs based on scientific literature.

### a. Database-to-Database Transmission ("E2B").

- Submit attachments to ICSRs through the electronic submission gateway (ESG). See page 32 of the document "[Specifications for Preparing and Submitting Electronic ICSRs and ICSR Attachments](/media/132096/download)" ([./media/132096/download](/media/132096/download)). (PDF - 204KB).

### b. Safety Reporting Portal (SRP).

- To submit ICSR attachments via the SRP, use the features within the portal that allows you to browse, select, and attach documents to an ICSR.

## 3. Submitting Periodic Safety Reports (PSR)

Periodic safety reports are comprised of a descriptive portion and non-expedited ICSRs (21 CFR 314.80 and 600.80), regardless of the format.

### 1. Descriptive Portion:

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- Use [Electronic Common Technical Document \(eCTD\)](/drugs/electronic-submissions-cder/electronic-common-technical-document-ectd) (</drugs/electronic-submissions-cder/electronic-common-technical-document-ectd>), specifications to submit the descriptive portion electronically.
- Indicate in the descriptive portion that the ICSRs have been submitted electronically as XML files to the FDA Electronic Submissions Gateway (ESG) or via the Safety Reporting Portal (SRP).

2. **Non-expedited ICSRs:** must be submitted as described above and on or before the periodic safety report due date. Do NOT submit expedited ICSRs previously submitted.

## Resources For You

- [FAQ: Combination Products](/media/131508/download) (</media/131508/download>). (PDF - 92 KB)
- [FAERS Submissions Frequently Asked Questions](/drugs/fda-adverse-event-reporting-system-faers/faers-submissions-frequently-asked-questions) (</drugs/fda-adverse-event-reporting-system-faers/faers-submissions-frequently-asked-questions>).
- [Public Meeting: Electronic Submission of Adverse Event Reports to FDA Adverse Event Reporting System \(FAERS\) using International Council for Harmonisation \(ICH\) E2B\(R3\) Standards](/drugs/news-events-human-drugs/electronic-submission-adverse-event-reports-fda-adverse-event-reporting-system-faers-using) (</drugs/news-events-human-drugs/electronic-submission-adverse-event-reports-fda-adverse-event-reporting-system-faers-using>).
- [FAQs: Safety Reporting Portal](/drugs/fda-adverse-event-reporting-system-faers/faqs-safety-reporting-portal) (</drugs/fda-adverse-event-reporting-system-faers/faqs-safety-reporting-portal>).



# Exhibit 48

*Specifications for Preparing and Submitting  
Electronic ICSRs and ICSR Attachments (April 2021)*

# Specifications for Preparing and Submitting Electronic ICSRs and ICSR Attachments

## *Technical Specifications Document*

### **Associated Guidance Documents and Conformance Guide:**

**Draft Guidance for Industry: Providing Submissions in Electronic Format –  
Postmarketing Safety Reports (June 2014)**

**Guidance for Industry and FDA Staff: Postmarketing Safety Reporting for  
Combination Products (July 2019)**

**Draft Guidance for Industry: Providing Regulatory Submissions in Electronic  
Format: IND Safety Reports (October 2019)**

**Electronic Submissions of IND Safety Reports Technical Conformance Guide  
(October 2019)**

For questions regarding this technical specifications document, contact the Office of Surveillance and Epidemiology, Center for Drug Evaluation and Research, Food and Drug Administration, at [FAERSESUB@fda.hhs.gov](mailto:FAERSESUB@fda.hhs.gov); or Office of Communication, Outreach and Development, Center for Biologics Evaluation and Research, Food and Drug Administration, at [CBERICSRSubmissions@fda.hhs.gov](mailto:CBERICSRSubmissions@fda.hhs.gov).

**U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)  
Center for Biologics Evaluation and Research (CBER)**

**April 2021**

# Specifications for Preparing and Submitting Electronic ICSRs and ICSR Attachments

**Revision History Table**

Date	Version	Summary of Changes
2008-06-11	1.0	Initial Version
2008-08-06	1.1	Added Filename format information
2008-10-10	1.2	Updated UTF-8 to ISO-8859-1 encoding; indicated simultaneous acceptance of ICSR and ICSR attachments; provided another acceptable file extension for SGML files; and clarified use of abbreviations (NDA, ANDA, and STN)
2008-10-22	1.3	Provided clarification in Section II; updated footnote 3; and added new paragraph to Section V.C.
2013-07-05	1.4	Updated AERS to FAERS migration changes, removed references to SGML file formatting, incorporated updates from CBER
2018-02-06	1.5	Added a new section to highlight data fields for reporting ICSRs on Combination Products
2019-09-30	1.6	<p>Added two new sections to provide regional data elements for electronic submissions of certain IND safety reports (section I) and IND-exempt Bioavailability (BA)/Bioequivalence (BE) studies (section J).</p> <p>Added an appendix (II) highlighting various case scenarios for electronic submissions of IND safety reports to FAERS.</p>

2020-02-11	1.7	<p>Added a new value to the data element B.4.k.1 for drug characterization to accommodate a similar device.</p> <p>Updated the data element B.4.k.18.2 to specify values.</p> <p>Updated the data element B.4.k.18.3 to use default value.</p>
2020-12-18	1.8	<p>Added a new regional data element A.1.FDA.16 (FDA Safety Report Type) in Table 2 Detailed Description of Administrative Tags</p> <p>Added section Submission Rules</p> <p>Added a new value to the data element B.4.k.1 and B.4.k.19 in section J. IND-exempt BA/BE Studies</p>
2021-03-26	1.9	<p>Updated section XML Header to include DTD 3.0 for premarketing reporting</p> <p>Updated the reference description to data element A.1.FDA.16 in Table 2 Detailed Description of Administrative Tags</p> <p>Updated section ICSR Message Header Information to include information in premarketing reporting</p> <p>Updated section AS2 Headers and Routing IDs for Premarketing Safety Report Submissions</p> <p>Updated section Submission Rules</p>

# *Specifications for Preparing and Submitting Electronic ICSRs and ICSR Attachments*

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## Specifications for Preparing and Submitting Electronic ICSRs and ICSR Attachments

This document provides current specifications for submitting individual case safety reports (ICSRs) and ICSR attachments in electronic form. The specifications apply to electronic submission of ICSRs for drug and biological products studied under an investigational new drug application (IND) (including bioequivalence studies conducted under IND), ICSRs from IND-exempt bioavailability (BA)/bioequivalence (BE) studies, and ICSRs for marketed drug and biological products and combination products to the FDA Adverse Event Reporting System (FAERS). The specifications do not apply to the following marketed biological products: prophylactic vaccines, whole blood or components of whole blood, human cells, tissues, and cellular and tissue-based products (HCT/Ps) regulated by FDA.

This document discusses the technical specifications for electronic submission of ICSRs and ICSR attachments through the FDA Electronic Submissions Gateway (ESG).<sup>1</sup> ICSRs (and any ICSR attachments) are to be prepared in accordance with the International Council for Harmonisation (ICH) E2B(R2) data elements in extensible markup language (XML) file format for compatibility with the FAERS database. ICSRs for marketed products should not be submitted to the electronic Common Technical Document (eCTD).<sup>2</sup>

If you have not previously submitted an ICSR in electronic format to FAERS, you should contact the FAERS electronic submission coordinator at [faersesub@fda.hhs.gov](mailto:faersesub@fda.hhs.gov) and they will assist you with submission of a test file.

### I. ELECTRONIC SUBMISSIONS OF ICSRS AND ICSR ATTACHMENTS

Each initial ICSR or follow-up ICSR may consist of structured information and non-structured information, such as ICSR attachments.

For the FDA to process, review, and archive the ICSRs, prepare your ICSRs for electronic submission by following these steps:

- Provide a unique filename for the submission; see section II of this document.
- Add a file header and file extension; see section IV of this document.
- Populate the elements of the ICSR file; see section V of this document.

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<sup>1</sup> For information on providing submissions using the ESG, refer to <https://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/default.htm>.

<sup>2</sup> See FAERS Electronic Submissions at <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm115894.htm>.

- If applicable, add ICSR attachments to ICSRs; see section VI of this document.

## II. SUBMISSION FILE NAME

Each electronic submission of ICSRs or attachments to ICSRs must have a unique filename (e.g., your named file + date and time stamp down to the second: filenameYYYYMMDDHHMMSS). You may choose your own format to maintain uniqueness.

## III. ICSR ACKNOWLEDGEMENTS

### A. ESG Acknowledgement

After submitting an ICSR or ICSR attachment, you should receive an ESG message delivery notice (MDN) notifying the sender of the receipt of their submission, but not acknowledging the acceptance of the submission. If the MDN is not received within 2 hours, go to the [ESG System Status](#) web page. If the ESG web page is non-operational, go to the [ESG Home Page](#) for further information.

### B. FAERS Acknowledgment

The MDN is then followed by a FAERS acknowledgment within 2 hours of the ESG acknowledgment. The FAERS acknowledgment notifies the sender whether their submission has been processed. If you do not receive the FAERS acknowledgment, resubmit the ICSRs without changing the filename.

If you receive a report acknowledgement code 02, indicating that your submission did not process due to file error/s that are specified in the acknowledgment, then proceed as follows:

- For submission with a single ICSR, resubmit the corrected ICSR with a new unique filename.
- For a submission consisting of multiple ICSRs, if one or more ICSRs in the submission failed to process, separate those ICSRs from the processed ICSRs, correct them and resubmit only the corrected ICSRs as a new submission with a unique filename. For example, if there were 50 ICSRs in an original submission and 15 of them failed to process, then only those 15 ICSRs must be separated, corrected appropriately, and resubmitted with a new unique filename. The resubmission should not contain any of the previously processed ICSRs.

## IV. ELECTRONIC TRANSPORT FORMAT: XML FILES

FDA accepts the data elements defined in the “Guidance for Industry E2BM Data Elements for

Transmission of Individual Case Safety Reports (April 2002).”<sup>3</sup> The ICH E2B(R2) guidance provides additional information and clarification of the previously issued guidances.<sup>4</sup>

The electronic transport format also known as the Document Type Definition (DTD) for XML files is described in the associated document “XML Formatted DTD” (DTD Version 2.1, DTD Version 2.2 and DTD Version 3.0) (see links to the documents below in section C).

#### **A. AS2 Headers and Routing IDs for Postmarketing Safety Report Submissions**

For postmarketing safety report submissions, the sponsors should include the unique AS2 headers or routing IDs for safety reports and attachments in one of the two ways listed below.

- AS2 Headers
  - Destination: “CDER”
  - XML files: AERS
  - PDF’s: AERS\_ATTACHMENTS

or

- Routing IDs
  - XML files: FDA\_AERS
  - PDF’s: FDA\_AERS\_ATTACHMENTS

#### **B. AS2 Headers and Routing IDs for Premarketing<sup>5</sup> Safety Report Submissions**

For premarketing safety report submissions, the sponsors should include the unique AS2 headers or routing IDs for premarketing safety reports and attachments, as listed below, to differentiate these reports between CDER and CBER, and from postmarketing ICSRs.

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<sup>3</sup> For information on Guidance for Industry on E2B Data Elements for Transmission of Individual Case Safety Reports, please refer to the following:

<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073092.pdf>

<sup>4</sup> See the guidance for industry entitled *E2B Data Elements for Transmission of Individual Case Safety Reports* (January 1998) (E2B). FDA currently supports use of E2B data elements in addition to the E2BM data elements. However, it is preferred that ICSRs be submitted with E2BM data elements to allow for the most efficient processing of the submissions. For those who wish to use E2B data elements and the corresponding electronic transport format (ICH M2 Electronic Transmission of Individual Case Safety Reports Message Specification Final Version 2.3 Document Revision February 1, 2001 (ICH ICSR DTD Version 2.1)), please refer to documentation provided at <https://www.fda.gov/downloads/drugs/ucm149932.pdf>

<sup>5</sup> The term premarketing safety report refers to IND safety reports and IND-exempt BA/BE studies safety reports.

**1. Submitting premarketing safety reports for CDER IND and IND-Exempt BA/BE**

- AS2 Headers
  - Destination: “CDER”
  - XML files: AERS\_PREMKT\_CD ER
  - PDF’s: AERS\_ATTACHMENTS\_PREMKT\_CD ER

or

- Routing IDs
  - XML files: FDA\_AERS\_PREMKT\_CD ER
  - PDF’s: FDA\_AERS\_ATTACHMENTS\_PREMKT\_CD ER

**2. Submitting premarketing safety reports for CBER IND**

- AS2 Headers
  - Destination: “CBER”
  - XML files: AERS\_PREMKT\_CBER
  - PDF’s: AERS\_ATTACHMENTS\_PREMKT\_CBER

or

- Routing IDs
  - XML files: FDA\_AERS\_PREMKT\_CBER
  - PDF’s: FDA\_AERS\_ATTACHMENTS\_PREMKT\_CBER

**C. XML Header**

The addition of an XML header enables FDA to process ICSRs in an XML format successfully. FDA supports only the ISO-8859-1 character set for encoding the submissions.

**1. For submissions of postmarketing safety reports for drug and biological products, add the following XML header to the ICSR file:**

<?xml version=“1.0” encoding=“ISO-8859-1”?>

<!DOCTYPE ichicsr SYSTEM “<https://www.accessdata.fda.gov/xml/icsr-xml-v2.1.dtd>”>

**2. For submissions of postmarketing safety reports for combination products, add the following XML header to the ICSR file:**

<?xml version=“1.0" encoding=“ISO-8859-1”?>

<!DOCTYPE ichicsr SYSTEM “<https://www.accessdata.fda.gov/xml/icsr-xml->

[v2.2.dtd](#)”>

**3. For submissions of premarketing safety reports, add the following XML header to the ICSR file:**

<?xml version=“1.0” encoding=“ISO-8859-1”?>

<!DOCTYPE ichicsr SYSTEM “<https://www.accessdata.fda.gov/xml/icsr-xml-v3.0.dtd>”>

#### **D. ICSR Message Header Information**

**1. For submissions of postmarketing drug and biological product safety reports, use the value “2.1” for the DTD Descriptor <messageformatversion>:**

<messageformatversion>2.1</messageformatversion>

**2. For submissions of postmarketing combination product safety reports, use the value “2.2” for the DTD Descriptor <messageformatversion>:**

<messageformatversion>2.2</messageformatversion>

**3. For submissions of premarketing safety reports, use the value “3.0” for the DTD Descriptor <messageformatversion>:**

<messageformatversion>3.0</messageformatversion>

#### **E. ICSR File Extension**

Use “xml” as the file extension for ICSRs in XML format. The name of the file should be 200 characters or less, excluding the three-digit extension. FDA does not support file names with multiple periods “.” or the use of any special or foreign characters except underscore “\_” and dash “-”.

### **V. DATA ELEMENTS FOR ELECTRONIC SUBMISSIONS**

#### **A. Minimum Data Elements Requirements**

For a submission to be successfully processed, submit an ICSR with the minimum data elements for reporting that are appropriate for the product type. If a sponsor submits an ICSR without the minimum data elements, they will receive a FAERS acknowledgement code 02 stating that the submission was not processed (see section III.B above). The minimum data elements for reporting are provided in Table 1 and the bullets that follow list the data elements to include in an ICSR by product type.

**Table 1. Minimum Data Elements**

Element	Data
B.1	Identifiable Patient
A.2	Identifiable Reporter
B.2	Reaction or Event
B.4	Suspect Drug Product

- Adverse event reports submitted for unapproved prescription drug products, unapproved nonprescription drug products and products approved for marketing under an abbreviated new drug application (ANDA), biologics license application (BLA), or new drug application (NDA), including combination products should have, at a minimum, the four data elements listed in Table 1.
- Adverse event reports for compounded drugs submitted by registered outsourcing facilities should have at a minimum, a suspect product and an adverse event.
- IND safety reports should include, at a minimum, the four data elements listed in Table 1 and the IND number under which the clinical trial where the event occurred is conducted.
- Serious adverse event reports from IND-exempt BA/BE studies should include, at a minimum, the four data elements listed in Table 1 and the pre-assigned ANDA number (hereafter referred as, Pre-ANDA number).

#### **B. Administrative and Identification Elements**

For FDA to successfully process your electronic ICSR submissions, populate the administrative and identification elements as indicated in Table 2.



**Table 2. Detailed Description of Administrative Tags\***

Element	DTD Descriptor 2.1	Length	Element Values for DTD 2.1
A.1.9	<fulfillexpeditecriteria>	1N	1= Yes (15-Day expedited) 2= No (non-expedited) 4= 5-Day 5= 30-Day 6= 7-Day expedited
A.1.0.1	<safetyreportid>	100AN	Sender's (Case) Safety Report Unique Identifier†
A.1.10.1	<authoritynumb>	100AN	Regulatory authority's case report number
A.1.10.2	<companynumb>	100AN	Other sender's case report number
A.3.1.2	<senderorganization>	60AN	Sender identifier
A.2.3.2^	<sponsorstudynumb>	35AN	IND or Pre-ANDA number under which the clinical trial where the event occurred is conducted
A.1.FDA.16††	<fdasafetyreporttype>	1N	1=IND Safety Report 2=IND-Exempt BA/BE Safety Report 3=Postmarketing Safety Report

\* Include either <companynumb> or <authoritynumb> values. FDA cannot process the ICSR without one of these element values.

† The Sender's Safety Report Unique Identifier is comparable to the Manufacturer Report Number (also referred to as the Manufacturer Control Number (MCN)) provided on paper in FDA Form 3500A. This number is the company's unique case identification number, which is used for the life of the case.

^ For IND and IND-exempt BA/BE study safety reports only. An IND-exempt BA/BE study refers to a BA/BE study not conducted under IND.

†† The FDA Safety Report Type data element distinguishes premarketing (IND and IND-Exempt BA/BE) safety reports from postmarketing safety reports and is used to determine which reports are posted publicly. The FDA Safety Report Type data element is optional when using DTD 2.1 and 2.2 for postmarketing safety report submission but is mandatory when using DTD 3.0 for premarketing safety report submission.

### C. Authorization/ Application Number Format

In the section designated for drug and biological products information, use the following format for the "Authorization/ Application Number" element (B.4.k.4.1) <drugauthorizationnumb> as indicated in Table 3 and described below.

- For approved drug and biological products marketed under an approved application, include the acronym "NDA" or "ANDA," followed by a space and then the number for the application (e.g., NDA 012345, ANDA 012345). For prescription drug products marketed without an approved application (Rx No Application), use "000000." For a nonprescription drug product marketed without an approved application (Non-Rx No

Application), use “999999.” For adverse event reports for compounded drug products submitted by registered outsourcing facilities, use “COMP99.”

- For marketed biological products, include the appropriate acronym “BLA,” “STN,” or “PLA” followed by a space and the primary six-digit number (e.g., STN 123456).

**Table 3. Detailed Description of Application Number Formats**

Type of Application	Recommended Format
NDA/ ANDA	NDA, ANDA 012345
STN/ BLA/ PLA	STN or BLA or PLA 123456
Rx No Application	000000
Non-Rx No Application	999999
Compounded Products	COMP99

#### **D. Unique Case Identification Numbers for Initial and Follow-Up ICSRs**

For the follow-up ICSR safety reports to be correctly linked to your initial ICSR report, follow these steps:

- Use the same <safetyreportid> for the E2BM elements in section A.1.0.1 for the initial ICSR and any of its follow-up ICSRs; this allows the follow-up report to be linked to the initial report in the FAERS database.
- If the initial ICSR was submitted on paper but its follow-up ICSR is submitted electronically, include the Manufacturer Control Number (MCN) listed in Box G9 of the FDA paper Form 3500A from the initial report in both A.1.0.1 <safetyreportid> and in A.1.10.2 <companynumb> field in the follow-up electronic submission.
- Always use the <safetyreportid> that was assigned to the initial ICSR when submitting follow-up reports. If you need to change the <safetyreportid> internally, note the internally reassigned <safetyreportid> in the narrative section of the follow-up report (i.e., element B.5.1) (e.g., “This ICSR has been reassigned to the Company ID number COA12345”). Do not use the internally reassigned <safetyreportid> for any follow-up reports.
- In the event that an incorrect <safetyreportid> has been used in a follow-up report, contact the FAERS electronic submission coordinator at [faersesub@fda.hhs.gov](mailto:faersesub@fda.hhs.gov) so that the follow-up ICSR can be matched to the initial ICSR.

#### **E. MedDRA Specific Elements**

Use the ICH Medical Dictionary for Regulatory Activities (MedDRA) to code medical

terminology.<sup>6</sup> When possible, use the Lowest Level Term (LLT), and record the LLT as the MedDRA numeric code rather than the LLT name (e.g., the LLT name is Rash; the MedDRA numeric code for LLT Rash is 10378444).

### **1. Reaction/Event**

#### **a) Reaction/Event as reported by the primary source field**

Record the original reporter's words verbatim and/or use short phrases to describe the reaction/event in element (B.2.i.0).

#### **b) Reaction/Event MedDRA Term LLT numeric code or text field**

Record the MedDRA LLT that most closely corresponds to the term reported by the original reporter in element (B.2.i.1).

#### **c) Reaction/Event MedDRA Preferred Term (PT) numeric code or text field**

Record the MedDRA PT that most closely corresponds to the term reported by the original reporter in element (B.2.i.2).

### **2. Other E2B Elements**

For the E2B elements listed in Table 4, use either MedDRA text or, preferably, the corresponding numeric code.

**Table 4. Additional E2B Elements for Preferred MedDRA Coding**

<b>Element</b>	<b>DTD Descriptor 2.1</b>	<b>Length</b>
B.1.7.1a.2	<patientepisodename>	250 AN
B.1.8f.2	<patientdrugindication>	250 AN
B.1.8g.2	<patientdrugreaction>	250 AN
B.1.9.2b	<patientdeathreport>	250 AN
B.1.9.4b	<patientdetermineautopsy>	250 AN
B.1.10.7.1a.2	<parentmedicalepisodename>	250 AN
B.1.10.8f.2	<parentdrugindication>	250 AN
B.1.10.8g.2	<parentdrugreaction>	250 AN
B.3.1c	<testname>	100 AN
B.4.k.11b	<drugindication>	250 AN
B.4.k.17.2b	<drugrecruration>	250 AN
B.4.k.18.1b	<drugreactionasses>	250 AN
B.5.3b	<senderdiagnosis>	250 AN

<sup>6</sup> Companies can license MedDRA from an international maintenance and support services organization (MSSO) (toll free number 877-258-8280; Direct 571-313-2574; fax 571-313-2345; e-mail MSSOhelp@mssotools.com).

## F. Drug Description and Case Narrative Elements

To ensure the successful processing of your electronic ICSR submission, applicants are advised to populate the drug description and narrative elements as indicated in Table 5.

**Table 5. Detailed Description of Drug(s) and Narrative Elements<sup>\*†</sup>**

Element	DTD Descriptor 2.1	Length	Element Values for DTD 2.1
B.4.k.1	<drugcharacterization>	1N	1=Suspect 2=Concomitant 3=Interacting 4=Drug not administered
B.4.k.2.1	<medicinalproduct>	70AN	Proprietary Medicinal Product Name
B.4.k.2.2	<activesubstancename>	100AN	Drug Substance Name
B.5.1	<narrativeincludeclinical>	20000AN	Case Narrative

<sup>\*</sup>Include <medicinalproduct> and/or <activesubstancename>. FDA cannot process the ICSR without at least one of these elements.

<sup>†</sup>Appendix I lists various examples of correct drug element formats.

### 1. Recording Multiple Drugs

If you are submitting safety reports for products containing multiple drugs, you should follow these steps:

- List the proprietary drug product name in element (B.4.k.2.1) and/or list the drug substance name in element (B.4.k.2.2).
- List the characterization of each reported drug's role, such as suspect, concomitant, interacting, drug not administered, or similar device in element (B.4.k.1).

### 2. Medicinal Product Name and Active Drug Substance Name

FDA validates medicinal product names to the available Structured Product Labeling (SPL)<sup>7</sup>, the submitted label (as ICSR attachment), and the Substance Registration System (SRS). These are further described below:

- When the product has an SPL, use the same naming convention as it appears in the SPL when submitting the ICSR.

---

<sup>7</sup> The SPL is a document markup standard approved by Health Level Seven (HL7) and adopted by FDA as a mechanism for exchanging product and facility information. See <https://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>.

- When submitting a product label as an attachment to an ICSR, use the name as it appears on the submitted product label.
- If no medicinal product is named and only the active substance is named, use the name of the active substance as it appears in the SRS.<sup>8</sup>

### **3. Case Narrative**

#### **a) Initial ICSR**

Record all case narrative information including clinical course, therapeutic measures, outcome, and all additional relevant information in element (B.5.1). If the information exceeds the field length, consider describing the information using fewer words.

Although the use of only the most widely used medical abbreviations is permissible if necessary, their use should be limited when possible.

#### **b) Follow-up ICSR**

Record both new information and corrections to previously submitted ICSRs in element (B.5.1).

## **G. Other Data Elements**

### **1. Dosage Information Field**

If dosage information cannot be captured in the structured fields in B.4.k.5, then use the element (B.4.k.6) <drugdosagetext>.

### **2. Pharmaceutical Form Field**

Record the pharmaceutical form in element (B.4.k.7) <drugdosageform>. FDA accepts the European Medicines Agency (EMA) dosage codes or text.<sup>9</sup>

### **3. Route of Administration Field**

Code the route of administration in element (B.4.k.8) <drugadministrationroute> as described in the ICH E2B(R2) guidance.

### **4. Receiver Field (A.3.2)**

Complete the receiver using the code or text listed in Table 6.

---

<sup>8</sup> <https://www.fda.gov/ForIndustry/DataStandards/SubstanceRegistrationSystem-UniqueIngredientIdentifierUNII/default.htm>.

<sup>9</sup> For a complete list of EMA dosage form codes and text, please refer to [https://www.ema.europa.eu/documents/other/list-pharmaceutical-dosage-forms\\_en.xls](https://www.ema.europa.eu/documents/other/list-pharmaceutical-dosage-forms_en.xls)

**Table 6. Receiver Information**

Element	DTD Descriptor 2.1	Code or Text
A.3.2.1	<receivertype>	2
A.3.2.2a	<receiverorganization>	FDA
A.3.2.2b	<receiverdepartment>	Office of Surveillance and Epidemiology
A.3.2.2d	<receivergivenname>	FAERS
A.3.2.3a	<receiverstreetaddress>	10903 New Hampshire Avenue
A.3.2.3b	<receivercity>	Silver Spring
A.3.2.3c	<receiverstate>	MD
A.3.2.3d	<receiverpostcode>	20993
A.3.2.3e	<receivercountrycode>	US
A.3.2.3f	<receiveremailaddress>	faersesub@fda.hhs.gov

### 5. Message Receiver Field (M.1.6)

The following two message receiver identifiers are used by FDA to distinguish between test and production submissions:

- Test ICSRs: <messagereceiveridentifier>ZZFDATST</messagereceiveridentifier>
- Production ICSRs: <messagereceiveridentifier>ZZFDA</messagereceiveridentifier>

## H. Data Elements for Electronic Submissions of Safety Reports for Postmarketing Combination Products

To ensure the successful processing of your electronic ICSR submission for a marketed drug- or therapeutic biologic led- combination product (e.g., a combination product containing a drug/biologic and device and marketed under an NDA or a BLA), you should populate the data elements indicated in Table 7.

Note: Some of the DTD descriptors listed in Table 7 are under existing E2B(R2) header elements, and some DTD descriptors are under new data elements. Those data element numbers that are new, have the word “FDA” incorporated into the number and are U.S.-specific regional elements related to reporting on combination products.



**Table 7. Combination Product Data Elements**

Data Element	DTD Descriptor 2.2	Title	Description	Length	Element Values for DTD 2.2	Notes
M.1.2	<messageformatversion>	Message Format Version	Version number of Message Format	3AN	2.2	Use value 2.2 if using icrsr-xml-v2.2.dtd Use value 2.1 if using icrsr-xml-v2.1.dtd
A.1	<safetyreport>	Header/ Entity	Identification of the case safety report			
A.1.9	<fulfillexpeditecriteria>	Does this case fulfill the local criteria for an expedited report		1N	1=Yes 2=No 4=5-Day 5=30-Day	Element values= 1 for 15-Day Expedited* and 2 for periodic non-expedited† Element value= 4 for remedial action to prevent an unreasonable risk of substantial harm to the public health Element value= 5 for malfunction with no associated adverse event Do not use element value of 3.
A.1.FDA.15	<combinationproductreport>	Combination Product Report Flag	Combination Product Report Flag	1N	1=Yes 2=No	
A.2	<primarysource>	Primary source(s) of information	Header/ Entity		Area below should be a repeatable block	

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Data Element	DTD Descriptor 2.2	Title	Description	Length	Element Values for DTD 2.2	Notes
A.2.1		Primary source(s)	Header			
A.2.1.3.FDA.4	<reporteremailaddress>	Reporter's Email Address		100AN		
B.1.1	<patientinitial>	Patient	Patient Identifier	10AN		If a single report is reported for a malfunction with no adverse event, the element value should be "NONE."  If there are multiple malfunction reports with no adverse event, then the element value should be "SUMMARY."
B.4	<drug>	Drug(s) Information	Header/ Entity		Area below should be a repeatable block	
B.4.k.1	<drugcharacterization>	Characterization of drug role		1N	1= Suspect 2= Concomitant 3= Interacting 5= Similar Device	If the product in the report is about a similar device, the element value should be 5=Similar Device.
B.4.k.2		Drug Identification	Header			
B.4.k.2.4.FDA.1a	<expirationdateformat>	Expiration date format	Product Expiration date	3N	102=CCYYMM DD 610=CCYYMM 602=CCYY	
B.4.k.2.4.FDA.1b	<expirationdate>	Expiration date	Product Expiration date	8N		

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Data Element	DTD Descriptor 2.2	Title	Description	Length	Element Values for DTD 2.2	Notes
B.4.k.2.FDA.5	<productavailableforevaluation>	Product available for evaluation	Indicate whether product is available for evaluation	1N	1=Yes 2=No 3=Return	
B.4.k.2.6.FDA.1a	<productreturndateformat>	Product return date format	Date Format	3N	102=CCYYMM DD 610=CCYYMM 602=CCYY	
B.4.k.2.6.FDA.1b	<productreturndate>	Product return date	Date when Product was returned	8N		
B.4.k.20.FDA.1	<brandname>	Brand Name	The trade or proprietary name of the device constituent part of the suspect combination product as used in product labeling or in the catalog	80AN		At least one of the 3 must be reported <brandname> or <commondevicecode> or <productcode> for the device constituent part
B.4.k.20.FDA.2	<commondevicecode>	Common Device Name	Generic or common name of the device constituent part of the suspect combination product or a generally descriptive name	80AN		At least one of the 3 must be reported <brandname> or <commondevicecode> or <productcode> for device constituent part
B.4.k.20.FDA.3	<productcode>	Product Code	Product code	3AN	<a href="http://www.acce">http://www.acce</a>	At least one of the 3 must be

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Data Element	DTD Descriptor 2.2	Title	Description	Length	Element Values for DTD 2.2	Notes
			assigned to the device constituent part based upon the medical device product classification		<a href="https://www.fda.gov/premarket/ftp/area/foiclass.zip">ssdata.fda.gov/premarket/ftp/area/foiclass.zip</a>	reported <brandname> or <commondevicecode> or <productcode> for device constituent part
B.4.k.20.FDA.4	<manufacturer>	Manufacturer	Header/ Entity			
B.4.k.20.FDA.4a	<manufacturername>	Device Manufacturer Name	Manufacturer name of the device constituent part of the suspect combination product	100AN		
B.4.k.20.FDA.4b	<manufactureraddress>	Manufacturer Address	Manufacturer address of the device constituent part of the suspect combination product	100AN		
B.4.k.20.FDA.4c	<manufacturercity>	Manufacturer City	Manufacturer city of the device constituent part of the suspect combination product	35AN		
B.4.k.20.FDA.4d	<manufacturerstate>	Manufacturer State	Manufacturer state of the device constituent part of the suspect combination product	40AN		

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Data Element	DTD Descriptor 2.2	Title	Description	Length	Element Values for DTD 2.2	Notes
B.4.k.20.FDA.4e	<manufacturercountry>	Manufacturer Country	Manufacturer country of the device constituent part of the suspect combination product	2AN	ISO3166	
B.4.k.20.FDA.5	<modelnumber>	Model Number	Model number of the device constituent part	30AN		
B.4.k.20.FDA.6	<catalognumber>	Catalog Number	Catalog number of the device constituent part	30AN		
B.4.k.20.FDA.7	<serialnumber>	Serial Number	Serial number of the device constituent part	30AN		
B.4.k.20.FDA.8	<udinumber>	Unique Identifier UDI#	Unique identifier of the device constituent part	50AN		
B.4.k.20.FDA.9a	<dateimplantedformat>	Device Implant Date Format	Date format of device implant in the patient	3N	102=CCYYMM DD 610=CCYYMM 602=CCYY	For medical devices that are implanted in the patient, provide the implant date or best estimate. If day is unknown, month and year are acceptable. If month and year are unknown, year is acceptable

Data Element	DTD Descriptor 2.2	Title	Description	Length	Element Values for DTD 2.2	Notes
B.4.k.20.FDA.9b	<dateimplanted>	Device Implant Date	Date of device implant in the patient	8N		For medical devices that are implanted in the patient, provide the implant date or best estimate. If day is unknown, month and year are acceptable. If month and day are unknown, year is acceptable
B.4.k.20.FDA.10a	<dateexplantedformat>	Device Explant Date Format	Date format of device explant from the patient	3N	102=CCYYMM DD 610=CCYYMM 602=CCYY	If an implanted device was removed from the patient, provide the explant date or best estimate. If day is unknown, month and year are acceptable. If month and day are unknown, year is acceptable
B.4.k.20.FDA.10b	<dateexplanted>	Device Explant Date	Date of device explant from the patient	8N		If an implanted device was removed from the patient, provide the explant date or best estimate. If day is unknown, month and year are acceptable. If month and day are unknown, year is acceptable
B.4.k.20.FDA.11a	<deviceage>	Approximate age of device/ product	Age of device constituent part	5N		
B.4.k.20.FDA.11b	<deviceageunit>	Approximate age unit of device/ device/	Age unit of device constituent part	3N	800=Decade 801=Year 802=Month	



Data Element	DTD Descriptor 2.2	Title	Description	Length	Element Values for DTD 2.2	Notes
		product			803=Week 804=Day 805=Hour	
B.4.k.20.FDA.12	<labeledsingleusedevice>	Single Use Device	Indicate whether the device constituent part was labeled for single use or not	1N	1=Yes 2=No	
B.4.k.20.FDA.13a	<devicemanufacturedateformat>	Device Manufacture Date Format	Device Manufacture Date format	3N	102=CCYYMM DD 610=CCYYMM 602=CCYY	
B.4.k.20.FDA.13b	<devicemanufacturedate>	Device Manufacture Date	Device Manufacture Date	8N		
B.4.k.20.FDA.14		Remedial action initiated/ Remedial action taken for the product	Header			
B.4.k.20.FDA.14.1 a	<remedialactionrecall>	Recall	Recall initiated	1N	1=Yes 2=No	
B.4.k.20.FDA.14.1 b	<remedialactionrepair>	Repair	Repair initiated	1N	1=Yes 2=No	
B.4.k.20.FDA.14.1 c	<remedialactionreplace>	Replace	Replace initiated	1N	1=Yes 2=No	
B.4.k.20.FDA.14.1 d	<remedialactionrelabel>	Relabeling	Relabeling initiated	1N	1=Yes 2=No	
B.4.k.20.FDA.14.1	<remedialactionnotify>	Notification	Notification	1N	1=Yes	

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Data Element	DTD Descriptor 2.2	Title	Description	Length	Element Values for DTD 2.2	Notes
e			initiated		2=No	
B.4.k.20.FDA.14.1 f	<remedialactioninspection>	Inspection	Inspection initiated	1N	1=Yes 2=No	
B.4.k.20.FDA.14.1 g	<remedialactionpatientmonitor>	Patient monitoring	Patient monitoring	1N	1=Yes 2=No	
B.4.k.20.FDA.14.1 h	<remedialactionmodifyadjust>	Modification/Adjustment	Modification/Adjustment initiated	1N	1=Yes 2=No	
B.4.k.20.FDA.14.1i	<remedialactionother>	Other	Other Remedial Action initiated	75AN		
B.4.k.20.FDA.15	<deviceusage>	Device Usage	Indicate the use of the device constituent part of the suspect combination product	1N	1=Initial Use of Device 2=Reuse 3=Unknown	
B.4.k.20.FDA.16	<deviceotnumber>	Device Lot Number	Lot number of the device constituent part of the suspect combination product	35AN		
B.4.k.20.FDA.17	<malfunction>	Malfunction	Malfunction of product	1N	1=Yes 2=No	
B.4.k.20.FDA.18		Follow-up type	Header			
B.4.k.20.FDA.18.1 a	<followupcorrection>	Correction	Correction	1N	1=Yes 2=No	
B.4.k.20.FDA.18.1 b	<followupadditionalinfo>	Additional information	Additional information	1N	1=Yes 2=No	
B.4.k.20.FDA.18.1	<followupresponsetoFDA>	Response to	Response to FDA	1N	1=Yes	

Data Element	DTD Descriptor 2.2	Title	Description	Length	Element Values for DTD 2.2	Notes
c		FDA request	request		2=No	
B.4.k.20.FDA.18.1 d	<followupdeviceevaluation>	Device Evaluation	Device Evaluation	1N	1=Yes 2=No	
B.4.k.20.FDA.19	<deviceproblemandevaluation>	Device Problem and evaluation codes	Header/ Entity		Area Below Should be a Repeatable Block	
B.4.k.20.FDA.19.1 a	<evaluationtype>	Evaluation Type	Type of problem and/or the evaluation	2N	01=Device Problem 02=Method 03=Result 04=Conclusion	
B.4.k.20.FDA.19.1 b	<evaluationvalue>	Evaluation Value	The FDA code value based on the respective evaluation type	6N		The value depends on the respective <evaluationtype>  If <evaluationtype> = 01 --> <a href="https://www.fda.gov/media/146825/download">https://www.fda.gov/media/146825/download</a>  If <evaluationtype> = 02 --> <a href="https://www.fda.gov/media/146827/download">https://www.fda.gov/media/146827/download</a>  If <evaluationtype> = 03 --> <a href="https://www.fda.gov/media/146828/download">https://www.fda.gov/media/146828/download</a>  If <evaluationtype> = 04 --> <a href="https://www.fda.gov/media/146829/download">https://www.fda.gov/media/146829/download</a>
B.4.k.20.FDA.20	<operatorofdevice>	Operator of	Operator of the	100AN		Use the value "Health"

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Data Element	DTD Descriptor 2.2	Title	Description	Length	Element Values for DTD 2.2	Notes
		the Device	Device			Professional” or “Lay User/Patient.” If none applicable, then specify the “Other” value

\* 21 CFR 314.80(c)(1) and 600.80(c)(1) use the term “15-day Alert reports.” In the combination product PMSR final rule (21 CFR 4.101), these reports are defined as “Fifteen-day reports.”

† Periodic non-expedited ICSRs are the reports required under 21 CFR 314.80(c)(2)(ii)(B) and 21 CFR 600.80(c)(2)(ii)(B) for serious, expected and nonserious adverse drug experiences.

### I. Data Elements for Electronic Submissions of IND Safety Reports

To ensure the successful processing of your electronic IND ICSR submission, you should populate the following data elements as described in Table 8.

**Table 8. Investigational New Drug Clinical Data Elements**

Data Element	DTD Descriptor 3.0	Title	Description	Field Length	Element Values for DTD 3.0	Notes
A.1.4	<reporttype>	Type of Report		1N	1=Spontaneous 2=Report from Study 3=Other 4=Not Available to Sender (unknown)	Element value= 2 for Report from Study
A.1.9	<fulfillexpeditecriteria>	Does this case fulfill the local criteria for an expedited report?		1N	1=Yes 2=No 4=5-Day 5=30-Day 6=7-Day	Element value=1 for 15-Day Expedited Element value= 6 for 7-Day Expedited
A.1.12	<linkreportnumb>	Identification Number of the report which is linked to this report		100AN		Used to link all individual cases (safetyreportid) that make up an IND Safety Report submitted as a result of an Aggregate Analysis as per 312.32(c)(1)(i)(C) or for several events

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Data Element	DTD Descriptor 3.0	Title	Description	Field Length	Element Values for DTD 3.0	Notes
						submitted as per (312.32(c)(1)(i)(B)) when a Narrative Summary Report is provided, this field should be populated in the IND Safety Report that contains the Narrative Summary Report.
A.2.3.1	<studyname>	Study Name		100AN	Study ID_\$Abbreviated Trial Name	The Study ID should be the same value used in the study tagging file format of the eCTD submission.
A.2.3.2	<sponsorstudynumb>	Sponsor Study Number		35AN	IND number under which the clinical trial where the event occurred is conducted  Use the "Parent" IND number* for reports submitted from an Aggregate Analysis as per (312.32(c)(1)(i)(C)) or for several events	Populate this field with the Primary IND in the first block and repeat block A.2 with elements A.2.3.2 and A.2.3.3 as noted below with element value= 5 for sponsor's other INDs evaluating suspect product (where applicable) Include the acronym "IND" followed by a space and then the IND



Data Element	DTD Descriptor 3.0	Title	Description	Field Length	Element Values for DTD 3.0	Notes
					submitted as per (312.32(c)(1)(i)(B)), from trials conducted under more than one IND	number for the application (e.g. IND 123456) See Appendix II (Case Scenarios) for additional information on how to submit reports from sponsor's other INDs (Cross-reporting).
A.2.3.3	<observestudytype>	Study type in which the Reaction(s)/ Event(s) were observed		1N	1= Clinical Trials 2= Individual Patient Use (e.g., 'Compassionate Use' or 'Named Patient Basis') 3= Other Studies (e.g., Pharmacoeconomics, Intensive Monitoring) 4= Report from	Required if element value for A.1.4 is 2=Report from Study  Repeat this field as needed with element value= 5 for each Cross-reported IND.  The first block of this element in the report must not be 5.  If element value 4 is chosen, then A.1.9= 1.  See Appendix II (Case

Data Element	DTD Descriptor 3.0	Title	Description	Field Length	Element Values for DTD 3.0	Notes
					Aggregate Analysis as per 312.32(c)(1)(i)(C) or for several events submitted as per 312.32(c)(1)(i)(B) if a Narrative Summary Report is provided	Scenarios) for additional information on how to submit reports from an Aggregate Analysis.
B.1.1	<patientinitial>	Patient Identifier		10AN	5= Cross-reported IND Safety Report	For a report from an Aggregate Analysis as per 312.32(c)(1)(i)(C) or for several events submitted as per 312.32(c)(1)(i)(B) if a Narrative Summary Report is provided, the element value should be "AGGREGATE"
B.4.k.2.1	<medicinalproduct>	Proprietary Medicinal Product Name		70AN		For investigational drug and biological products without an established name (i.e. INN or USAN

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Data Element	DTD Descriptor 3.0	Title	Description	Field Length	Element Values for DTD 3.0	Notes
						name), prior to submitting IND safety reports to FAERS, the sponsor should submit a clinical information amendment to the IND, listing the names of the active drug substance/s and the medicinal product as they will be reported in E2B file submissions. The names should fit within the established E2B character length limits. Use company product code if no established name, for multi-ingredient products, or if name exceeds character length
B.4.k.2.2	<activesubstancename>	Active Drug Substance Names		100AN		
B.4.k.18	<drugreactionrelatedness>	Relatedness of Drug to				For IND Safety Reports, at least one suspect

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Data Element	DTD Descriptor 3.0	Title	Description	Field Length	Element Values for DTD 3.0	Notes
		Reaction/ Event				product should have relatedness of drug to reaction/ event
B.4.k.18.1a	<drugreactionassesmeddra version>	MedDRA Version for Reaction Assessed		8AN		
B.4.k.18.1b	<drugreactionasses>	Reaction Assessed		250AN		
B.4.k.18.2	<drugassessmentsource>	Source of Assessment		60AN		Use the value "Sponsor" or "Investigator". Include sponsor and investigator assessment when reporting both in separate blocks
B.4.k.18.3	<drugassessmentmethod>	Method of Assessment		35AN		Use the value "FDA".
B.4.k.18.4	<drugresult>	Result		35AN	1= Suspected 2= Not suspected	For IND Safety Reports, at least one suspect product should have relatedness of drug to reaction/ event
B.5.1	<narrativeincludeclinical>	Case Narrative Including Clinical		20,000 AN		FDA strongly encourages sponsors to construct narratives that fit within the ICH E2B character

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Data Element	DTD Descriptor 3.0	Title	Description	Field Length	Element Values for DTD 3.0	Notes
		Course, Therapeutic Measures, Outcome, and Additional Relevant Information				limit of 20,000 AN. If your narrative exceeds this limit, sponsors should include as much of the narrative as possible in this field and submit an ICSR attachment for any text that exceeds the character limit. Sponsors should not submit an ICSR attachment containing the entire narrative and leave the case narrative field empty. For reports from Aggregate Analysis as per 312.32(c)(1)(i)(C) or for several events submitted as per 312.32(c)(1)(i)(B) where PDF is attached, put “see attached Narrative Summary Report” in this field.

Data Element	DTD Descriptor 3.0	Title	Description	Field Length	Element Values for DTD 3.0	Notes
B.5.4	<sendercomment>	Sender's Comments		2000 AN		Identification and analysis of previously submitted events (as required by 312.32(c)(1)) should be reported in this field.

\*The "parent IND" is the IND under which clinical investigations were initiated in the United States. (If the drug is being evaluated in multiple INDs, this is generally the IND with the lowest number.) NOTE: This may not be the same as the first A.2.3.2 block if the drug is being evaluated under multiple INDs.

NOTE: See [FAERS Webpage](#) for case scenario examples for reporting IND safety reports (e.g., IND safety reports where the sponsor is evaluating suspect product under more than one IND, IND safety reports that are a result of an aggregate analysis, and IND safety reports with unapproved and approved drugs listed as suspect products).

**J. Data Elements for Electronic Submissions of ICSRs from IND-Exempt Bioavailability (BA)/ Bioequivalence (BE) Studies**

For successful processing of your electronic ICSRs submissions for a BA/BE study not conducted under an IND, you should populate the following data elements as described in Table 9.

**Table 9. Data Elements for IND-Exempt BA/BE Studies**

Data Element	DTD Descriptor 3.0	Title	Description	Field Length	Element Values for DTD 3.0	Notes
A.1.4	<reporttype>	Type of Report		1N	1=Spontaneous 2=Report from Study 3=Other 4=Not Available to Sender (unknown)	Element value=2 for Report from Study



Data Element	DTD Descriptor 3.0	Title	Description	Field Length	Element Values for DTD 3.0	Notes
A.1.9	<fulfillexpeditecriteria>	Does this Case Fulfill the Local Criteria for an Expedited Report?		1N	1=Yes 2=No 4=5-Day 5=30-Day 6=7-Day	Element value=1 for 15-Day Expedited Or Element value=6 for 7-Day Expedited
A.2.3.1	<studynum>	Study Name		100AN	Abbreviated Trial Name	
A.2.3.2	<sponsorstudynumb>	Sponsor Study Number		35AN	Pre-ANDA number for the IND-Exempt BA/BE Studies	Include the acronym "Pre-ANDA" followed by a space and then the Pre-ANDA number for the application (e.g. Pre-ANDA 123456)
A.2.3.3	<observestudytype>	Study Type in Which the Reaction(s)/ Event(s) were Observed		1N	1= Clinical Trials  2= Individual Patient Use (e.g., 'Compassionate Use' or 'Named Patient Basis')  3= Other Studies (e.g., Pharmacoeconomics, Pharmacoeconomics, Intensive Monitoring)  4= Report from Aggregate Analysis as per 312.32(c)(1)(i)(C) or for	Element value="1" for Clinical Trials.

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Data Element	DTD Descriptor 3.0	Title	Description	Field Length	Element Values for DTD 3.0	Notes
					Several Events Submitted as per 3 12.32(c)(1)(i)(B) if a Narrative Summary Report is Provided  5= Cross-Reported IND Safety Report	
B.4.k.2.1	<medicinalproduct>	Proprietary Medicinal Product Name		70AN		
B.4.k.1	<drugcharacterization>	Characterization of drug role		1N	1 = Suspect 2 = Concomitant 3 = Interacting 4 = Drug not administered	For no exposure to a study drug use 4=Drug not administered
B.4.k.2.2	<activesubstancename>	Active Drug Substance Name		100AN		
B.4.k.19	<drugadditional>	Additional Information on Drug		100AN	1 = Test drug 2 = Reference drug 3 = Placebo/Vehicle 4 = Control (negative or positive) 5 = Other drug	Specify whether the product exposed is the Test drug, Reference drug, Placebo, Vehicle, Control or Other drug

## **VI. ELECTRONIC FORMAT FOR ICSR ATTACHMENTS**

FDA can accept and archive ICSR attachments in PDF format. Currently approved formats for the non-structured component of an ICSR, such as ICSR attachments, are PDF versions 1.4 (current ICH standard) or 1.6 (current version in use at FDA). An ICSR attachment should be electronically submitted to FAERS after the associated ICSR has been submitted and accepted by FAERS.

### **A. Converting the ICSR Attachment to PDF**

Applicants should provide an individual PDF file for each ICSR attachment. If you are submitting multiple ICSR attachments for a particular ICSR, include each attachment in the same PDF file and provide a PDF bookmark to distinguish each attachment. For example, if you are submitting a hospital discharge summary and an autopsy report for a single ICSR, include both in a single PDF file with a bookmark to the hospital discharge summary and a bookmark to the autopsy report.

### **B. Identification Information in the PDF Document Information Fields**

Each PDF file contains fields to be completed by the author of the document. FAERS uses these fields to locate and retrieve the attachments to specific ICSRs. To enable FDA to match the attachment(s) to the correct ICSR, applicants should fill in the PDF document information fields with the appropriate E2B(R2) data elements for the ICSR as indicated in Table 10.

**Table 10. Document Information Fields in ICSR Attachments**

PDF Document Information Field	Include/Optional	Document Information*	Length
Title	Include	A.1.0.1 <safetyreportid> Sender's (Case) Safety Report Unique Identifier	100AN
Subject	Include	A.1.10.1 <authoritynumb> Regulatory Authority's Case Report Number OR A.1.10.2 <companynumb> Other Sender's Case Report Number	100AN
Author	Optional	A.1.11.2 <duplicatenumb> Other Identification Number	100AN
Keywords	Optional	A.1.7b <receiptdate> Date of Receipt of the Most Recent Information for this ICSR	8N

\* The information refers to the data elements in E2B(R2)

In addition:

- Use the ISO-8859-1 character set for the information fields.
- Do not exceed the character length indicated above for each information field.
- Avoid creating any custom fields with names identical to the information fields listed in Table 10.

If you need assistance, you can contact the FAERS electronic submission coordinator at [faersesub@fda.hhs.gov](mailto:faersesub@fda.hhs.gov).

## VII. SUBMISSION RULES

The submission rules define the condition that shall result in a negative acknowledgement and not be accepted by FAERS.

**Table 111. Submission Rules and Acknowledgement Status**

<b>Data Element</b>	<b>DTD Descriptor 2.1/2.2/3.0</b>	<b>Rejection Rule Description</b>	<b>Acknowledgement</b>
NA	NA	ICSR submitted via AS2 Header where XML file: AERS  or Routing ID where XML file: FDA_AERS and using DTD 3.0	reportacknowledgmentcode (B.1.8) = 02
NA	NA	ICSR submitted via AS2 Header where XML file: AERS_PREMKT  or Routing ID where XML file: FDA_AERS_PREMKT and using DTD 2.1 or 2.2	reportacknowledgmentcode (B.1.8) = 02
A.1.FDA.16	<fdasafetyreporttype>	ICSR submitted via AS2 Header where XML file: AERS_PREMKT  or Routing ID where XML file: FDA_AERS_PREMKT using DTD 3.0 and data value is empty	reportacknowledgmentcode (B.1.8) = 02
A.2.3.2	<sponsorstudynumb>	ICSR submitted via AS2 Header where XML file: AERS_PREMKT  or Routing ID where XML file: FDA_AERS_PREMKT using DTD 3.0 and data value is empty or not prefixed with 'IND' or 'Pre- ANDA'	reportacknowledgmentcode (B.1.8) = 02

# APPENDIX I. EXAMPLES OF CORRECT AND INCORRECT APPLICATION NUMBER AND DRUG ELEMENT FORMATS

Table 122. Examples of Application Number Formats and Drug Element Formats

	Examples of Application Number Format	Comment
Correct	<drugauthorizationnumb>NDA 012345</drugauthorizationnumb>	
Correct	<drugauthorizationnumb>BLA 123456</drugauthorizationnumb>	
Correct	<drugauthorizationnumb>NDA 012345</drugauthorizationnumb> <drugauthorizationholder>COMPANYX</drugauthorizationholder>	
Incorrect	<drugauthorizationnumb>123456/10300</drugauthorizationnumb>	Use the appropriate prefix for the NDA/ ANDA/ STN/ BLA/ PLA. Do not include additional data after the application number
Incorrect	<drugauthorizationnumb>NDA 12-345;IND12,345</drugauthorizationnumb>	Omit hyphens and commas in the application number. Do not populate the tag with two application numbers
Incorrect	<drugauthorizationnumb>OTC Product</drugauthorizationnumb>	For a non-prescription drug product marketed without an approved application (Non-Rx No Application), use "999999"
Incorrect	<drugauthorizationnumb>NDA 012345(COMPANYX)</drugauthorizationnumb> <drugauthorizationholder></drugauthorizationholder>	Do not populate the company name in the <drugauthorizationnumb> tag

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Examples of Application Number Format		Comment
Correct	<p>&lt;medicinalproduct&gt;TYLENOL&lt;/medicinalproduct&gt;          &lt;activesubstancename&gt;ACETAMINOPHEN&lt;/activesubstancename&gt;</p>	
Correct	<p>&lt;medicinalproduct&gt;MIRACLE WONDER DRUG&lt;/medicinalproduct&gt;          &lt;activesubstancename&gt;ACETAMINOPHEN&lt;/activesubstancename&gt;</p>	
Incorrect	<p>&lt;medicinalproduct&gt;AMAZING DRUG <b>OTC</b>@&lt;/medicinalproduct&gt;          &lt;activesubstancename&gt;ACETAMINOPHEN <b>500 mg</b>&lt;/activesubstancename&gt;</p>	
Incorrect	<p>&lt;medicinalproduct&gt;NEW DRUG <b>40 mcg/mL</b>&lt;/medicinalproduct&gt;          &lt;activesubstancename&gt;NEWSUBSTANCE <b>Inj</b> &lt;/activesubstancename&gt;</p>	
Incorrect	<p>&lt;medicinalproduct&gt;<b>MWD</b>&lt;/medicinalproduct&gt;          &lt;activesubstancename&gt;<b>APAP</b>&lt;/activesubstancename&gt;</p>	Do not use abbreviations for the brand name or active substance in the <medicinalproduct> and <activesubstance> tags

## APPENDIX II. CASE SCENARIOS FOR IND SAFETY REPORTS SUBMITTED TO FAERS

The following case scenarios are intended to provide examples to sponsors on the use of ICH E2B data standard elements for submission of IND safety reports to FAERS that may differ from postmarketing safety reports.

1. For any IND safety report where the sponsor is evaluating the suspect product under more than one IND (i.e. “Cross-reporting”)
  - a. Repeat block A.2 for each IND
    - i. Use first block A.2 to designate IND where the event occurred = “primary IND”
      1. A.2.3.2 = primary IND
      2. A.2.3.3 = data value could either be 1, 2, 3, or 4
      3. Other relevant information for the report to be populated in block A.2
    - ii. Repeat block A.2 as many times as needed with only the following data elements for each IND that the sponsor holds where that suspect product is being evaluated:
      1. A.2.3.2 = IND number for each cross-reported IND
      - and
      2. A.2.3.3 = 5

**Table 133. Case Scenario 1. For IND Safety Reports Submitted to FAERS**

Data Element	DTD Descriptor 3.0	Title	Element Values for DTD
A.2.3.2	<sponsorstudynumb>	Sponsor Study Number	IND number under which the Clinical Trial where the event occurred is conducted

Data Element	DTD Descriptor 3.0	Title	Element Values for DTD
A.2.3.3	<observestudytype>	Study Type in Which the Reaction(s) were observed	<p>1= Clinical Trial</p> <p>2= Individual Patient Use (<i>e.g.</i> ‘<i>Compassionate Use</i>’ or ‘<i>Named Patient Basis</i>’)</p> <p>3= Other Studies (<i>e.g.</i> <i>Pharmacoepidemiology, Pharmacoeconomics, Intensive Monitoring</i>)</p> <p>4= Report from Aggregate Analysis 312.32(c)(1)(i)(C) or for several events submitted as per 312.32(c)(1)(i)(B) if a Narrative Summary report is provided.</p> <p>5=Cross-reported IND safety report</p>

2. For an IND safety report that is a result of an aggregate analysis as per 312.32(c)(1)(i)(C) or for several events submitted as per 312.32(c)(1)(i)(B) if a narrative summary report is provided:

- a. Submit one IND safety report with the IND where the event occurred in A.2.3.2 <sponsorstudynumb> (or the “parent” IND if the events occurred in multiple INDs).

For this IND safety report, populate the data elements below in addition to other relevant information regarding the event and suspect product.

- i. Use data element = 4 in A.2.3.3<observestudytype>
  - ii. Use the term “AGGREGATE” in B.1.1 <patientinitial>
- b. Section VII.A.2. of the *FDA Guidance for Industry – “Safety Reporting Requirements for INDs and BA/BE Studies”* (December 2012) discusses several submission requirements for IND safety reports that are a result of an aggregate analysis. The following two sections describe these submission elements and how they are accomplished with electronic submission to FAERS.

1. The guidance states that IND safety reports that are a result of an aggregate analysis should contain a narrative description of the event and the results of the analysis (hereafter referred to as a “narrative

summary report”). For IND reports submitted to FAERS, attach the narrative summary report to the IND safety report as a PDF attachment (do not put the narrative summary report in the E2B narrative field).

- a. These instructions also apply to several events submitted as per 312.32(c)(1)(i)(B) if a narrative summary report is provided.
2. The guidance states that all the individual cases that were analyzed in the aggregate analysis should be submitted. Use the repeatable block A.1.12 to link all the safety report numbers for the individual supportive ICSRs (i.e. the numbers in A.1.0.1 for all the individual cases that are summarized in the narrative summary report).
  - a. These instructions also apply to several events submitted as per 312.32(c)(1)(i)(B) if a narrative summary report is provided.
  - b. IND safety reports previously submitted as ICSRs to FAERS do not have to be resubmitted (place the safety report numbers for these previously submitted reports in A.1.12).
  - c. For IND safety reports previously submitted in eCTD format, the sponsor should list the eCTD sequence number and date of submission in the narrative summary report. (The eCTD sequence number is the unique four-digit number for each IND submission the sponsor submits in the us-regional.xml file for the eCTD submission.)
  - d. IND safety reports previously submitted on paper should be attached to the IND safety report as PDF attachments.

**Table 144. Case Scenario 2. For IND Safety Reports Submitted to FAERS**

<b>Data Element</b>	<b>DTD Descriptor 3.0</b>	<b>Title</b>	<b>Element Values for DTD</b>
A.1.12	<linkreportnumb>	Identification number of the report(s) which are linked to this report	Used to link all individual cases (safetyreportid) that make up an IND Safety Report submitted as a result of an Aggregate Analysis as per 312.32(c)(1)(i)(C) or for several events submitted as per 312.32(c)(1)(i)(B) if a narrative summary report is provided
A.2.3.2	<sponsorstudynumb>	Sponsor Study Number	IND number under which the Clinical Trial where the event occurred is conducted

Data Element	DTD Descriptor 3.0	Title	Element Values for DTD
A.2.3.3	<observestudytype>	Study Type in Which the Reaction(s) were Observed	<p>1= Clinical Trials</p> <p>2= Individual Patient Use (<i>e.g.</i> ‘<i>Compassionate Use</i>’ or ‘<i>Named Patient Basis</i>’)</p> <p>3= Other Studies (<i>e.g.</i> <i>Pharmacoepidemiology, Pharmacoeconomics, Intensive Monitoring</i>)</p> <p>4= Report from Aggregate Analysis 312.32(c)(1)(i)(C)</p> <p>5=Cross-reported IND safety report</p>
B.1.1	<patientinitial>	Patient Identifier	For a Report from an Aggregate Analysis, the element value should be “AGGREGATE”

3. For adverse events that occur with a marketed drug being evaluated under an IND that meets both IND and post-marketing safety reporting requirements (21 CFR 312.32 and 314.80, 600.80, or 310.305), sponsors must submit two separate ICSRs:
- a. for the marketed drug for the NDA/BLA
  - and
  - b. for the study drug for the IND (IND number in A.2.3.2)

### APPENDIX III. CASE SCENARIOS FOR SAFETY REPORTS FROM IND-EXEMPT BA/BE STUDIES TO FAERS

Table 15 illustrates the ICH E2B data elements and element values for each IND-exempt BA/BE study exposure scenario described below:

#### Scenario 1: Exposure to a *study drug*:

This scenario applies to all drugs specified in the study protocol. For example, if a BA/BE study protocol for a generic opiate includes administration of naltrexone to each study subject prior to administration of a test or reference drug, naltrexone is a *study drug*, although it is not the test or reference drug. Similarly, a selective 5-HT<sub>3</sub> receptor antagonist to prevent nausea and vomiting is considered a *study drug* if the BA/BE study protocol states that the drug is administered to each study subject prior to administration of a test or reference drug.

#### Scenario 2: Exposure to an *other drug*:

*Other drugs* are drugs taken by or administered to a subject that are not part of study conduct per protocol. For example, a subject with a diagnosis of hypertension has normal blood pressure while treated with a beta blocker. The subject meets study enrollment criteria and continues to take his beta blocker during study participation. In this situation, the beta blocker is an *other drug*. Similarly, if a subject develops symptoms of heartburn during participation in a BA/BE study and is permitted, by the investigator, to use a nonprescription antacid or H<sub>2</sub> blocker for symptomatic relief, the nonprescription drug taken by the subject is an *other drug*.

#### Scenario 3: No exposure to a study drug:

A serious adverse event a subject experiences after enrollment to the study, but prior to exposure to a study drug, is subject to the expedited safety reporting requirement. To report a serious adverse event with no study drug exposure, the submitter should select values as shown in the Table 15, Scenario 3.



**Table 155. ICH E2B Data Element & Value Selections for IND-Exempt BA/BE Study Exposures**

Drug Exposure Scenario	Data Element	Element Values
Scenario 1: Exposure to a <i>study</i> <i>drug</i>	B.4.k.1	Select one element value
	B.4.k.2.1	Proprietary medicinal product name
	B.4.k.2.2	Drug substance name
	B.4.k.19	Select one from the following: 1 = Test drug 2 = Reference drug 3 = Placebo/Vehicle 4 = Control (negative or positive)
Scenario 2: Exposure to an <i>other</i> <i>drug</i>	B.4.k.1	Select one element value
	B.4.k.2.1	Proprietary medicinal product name
	B.4.k.2.2	Drug substance name
	B.4.k.19	5 = Other drug
Scenario 3: No exposure to a <i>study</i> <i>drug</i>	B.4.k.1	4 = Drug not administered
	B.4.k.2.1	Proprietary medicinal product name
	B.4.k.2.2	Drug substance name
	B.4.k.19	1 = Test drug

# Exhibit 49

Declaration of Dr. Tyler Johnson

IN THE UNITED STATES DISTRICT COURT  
FOR THE NORTHERN DISTRICT OF TEXAS  
AMARILLO DIVISION

**ALLIANCE FOR HIPPOCRATIC  
MEDICINE**, on behalf of itself, its members,  
and their members, and their members'  
patients; **AMERICAN ASSOCIATION OF  
PRO-LIFE OBSTETRICIANS AND  
GYNECOLOGISTS**, on behalf of itself, its  
members, and their patients; **AMERICAN  
COLLEGE OF PEDIATRICIANS**, on  
behalf of itself, its members, and their  
patients; **CHRISTIAN MEDICAL &  
DENTAL ASSOCIATIONS**, on behalf of  
itself, its members, and their patients;  
**SHAUN JESTER, D.O.**, on behalf of  
himself and his patients; **REGINA FROST-  
CLARK, M.D.**, on behalf of herself and her  
patients; **TYLER JOHNSON, D.O.**, on  
behalf of himself and his patients; and  
**GEORGE DELGADO, M.D.**, on behalf of  
himself and his patients,  
Plaintiffs,

v.

**U.S. FOOD AND DRUG  
ADMINISTRATION; ROBERT M.  
CALIFF, M.D.**, in his official capacity as  
Commissioner of Food and Drugs, U.S. Food  
and Drug Administration; **JANET  
WOODCOCK, M.D.**, in her official capacity  
as Principal Deputy Commissioner, U.S.  
Food and Drug Administration **PATRIZIA  
CAVAZZONI, M.D.**, in her official capacity  
as Director, Center for Drug Evaluation and  
Research, U.S. Food and Drug  
Administration; **U.S. DEPARTMENT OF  
HEALTH AND HUMAN SERVICES**; and  
**XAVIER BECERRA**, in his official capacity  
as Secretary, U.S. Department of Health and  
Human Services,  
Defendants.

Case No. \_\_\_\_\_

### **DECLARATION OF DR. TYLER JOHNSON**

I, Tyler Johnson, D.O., a citizen of the United States and a resident of Leo, Indiana, declare under penalty of perjury under 28 U.S.C. § 1746 that the following is true and correct to the best of my knowledge.

1. I am over eighteen years old and make this declaration on personal knowledge.
2. I received my Bachelor of Science in Biology from the University of Saint Francis in Fort Wayne. I attended medical school at the Lake Erie College of Osteopathic Medicine. My residency was at Michigan State University's Kalamazoo Center for Medical Studies.
3. I am an emergency department physician certified by the American Board of Emergency Medicine. I practice in the emergency departments of hospitals in northern Indiana. My practice includes treating patients throughout rural northern Indiana into the inner-city of Fort Wayne. I am also the director of emergency medicine at Parkview Dekalb Hospital.
4. I am a member of the American Association of Pro-Life Obstetricians and Gynecologists (AAPLOG).
5. I am familiar with the U.S. Food and Drug Administration's (FDA) Risk Evaluation and Mitigation Strategy (REMS) drug safety program. I am also familiar with the REMS issued by the FDA for the chemical abortion drugs mifepristone and misoprostol in 2016.

6. The FDA's 2016 REMS for mifepristone and misoprostol expanded the acceptable gestational age for chemical abortion, eliminated the in-person administration requirement for these dangerous drugs, eliminated mandatory post-abortion follow-up visits, and eliminated the requirement for prescribers to report all non-fatal adverse events.
7. The FDA's actions harm both women and practitioners.
8. Mifepristone and misoprostol are dangerous drugs that have serious effects on a woman's body. Without the medical supervision, women taking these drugs are at risk of serious and life-threatening complications and even death.
9. I have seen at least a dozen cases of life-threatening complications from the use of abortifacient drugs over the years. These emergency situations are becoming more common as more women are turning to chemical abortion as the FDA has relaxed its regulations.
10. In one case, for example, I treated a woman in the emergency department who had been given an abortion pill from a clinic in Chicago. She took the pill and began to experience heavy bleeding on the drive back to Fort Wayne. By the time she arrived at the hospital, she was unconscious. I performed emergent treatment and gave her a necessary blood transfusion. The patient required further evaluation and observation in the hospital. I have seen multiple cases similar to this one.

11. About a month ago, I treated an 18-year-old woman in the emergency department who was experiencing severe pain. Although the situation was not life-threatening to her, she was terrified, and it was clear to me that she did not understand what she had been given. It is not uncommon for women who take mifepristone and misoprostol to come to the emergency department because the pain is so terrible.
12. Many of the patients I have treated for complications with chemical abortion experience trauma. They usually have no follow-up with the doctors who prescribed or dispensed the abortifacient drugs, and they are not adequately prepared to understand what the drugs will do to them. In these situations, it is clear to me that these women and girls could not have given informed consent to chemical abortion.
13. In many cases, women are hesitant to tell us that they have taken chemical abortion drugs. On multiple occasions I have treated women in the emergency department who are experiencing extremely heavy bleeding even after they have already passed the unborn child. The women will sometimes eventually explain that they took abortifacient drugs, which helps us understand what is happening to them. I understand that many women are told by staff at the dispensing clinics to tell emergency department doctors that they are experiencing a “miscarriage.”
14. Because of the FDA’s relaxed regulation of these dangerous drugs, it is extremely easy for women to obtain mifepristone and misoprostol with little



or no supervision. This leaves emergency physicians like me to deal with preventable emergent and life-threatening situations after these women have taken these drugs. The unsupervised administration of chemical abortion drugs simply harms women and physicians.

15. The FDA's actions have created a culture of chaos for emergency room physicians. In my experience, patients who are given abortifacient drugs at clinics do not understand what they have taken and are often reluctant to tell emergency doctors what they have taken. This puts me and my colleagues in a position where we have to treat women in emergency situations without crucial information. This culture puts us in increasingly higher risk situations, which increases our exposure to claims of malpractice and liability.

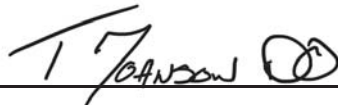
16. The increase in women presenting in the emergency department for complications with chemical abortions harms other patients too. Because more women are unnecessarily presenting in the emergency department, more of my time and attention is taken away from other patients who need it.

17. I also believe the FDA's elimination of reporting requirements for non-fatal adverse events harms women and practitioners. I believe we are not tracking these medications closely enough to know the extent of the negative side-effects commonly experienced. This also harms physicians' ability to practice evidence-based medicine. Moreover, women and girls cannot give informed

consent to chemical abortion when they do not receive accurate information about the risks associated with mifepristone and misoprostol.

18. Given my experience, I expect to see and treat more patients presenting themselves with complications from chemical abortion.

Executed this November 11, 2022.

By:   
Tyler Johnson, D.O.

# Exhibit 50

Declaration of Dr. Regina Frost-Clark

IN THE UNITED STATES DISTRICT COURT  
FOR THE NORTHERN DISTRICT OF TEXAS  
AMARILLO DIVISION

**ALLIANCE FOR HIPPOCRATIC  
MEDICINE**, on behalf of itself, its members,  
and their members, and their members'  
patients; **AMERICAN ASSOCIATION OF  
PRO-LIFE OBSTETRICIANS AND  
GYNECOLOGISTS**, on behalf of itself, its  
members, and their patients; **AMERICAN  
COLLEGE OF PEDIATRICIANS**, on  
behalf of itself, its members, and their  
patients; **CHRISTIAN MEDICAL &  
DENTAL ASSOCIATIONS**, on behalf of  
itself, its members, and their patients;  
**SHAUN JESTER, D.O.**, on behalf of  
himself and his patients; **REGINA FROST-  
CLARK, M.D.**, on behalf of herself and her  
patients; **TYLER JOHNSON, D.O.**, on  
behalf of himself and his patients; and  
**GEORGE DELGADO, M.D.**, on behalf of  
himself and his patients,  
Plaintiffs,

v.

**U.S. FOOD AND DRUG  
ADMINISTRATION; ROBERT M.  
CALIFF, M.D.**, in his official capacity as  
Commissioner of Food and Drugs, U.S. Food  
and Drug Administration; **JANET  
WOODCOCK, M.D.**, in her official capacity  
as Principal Deputy Commissioner, U.S.  
Food and Drug Administration **PATRIZIA  
CAVAZZONI, M.D.**, in her official capacity  
as Director, Center for Drug Evaluation and  
Research, U.S. Food and Drug  
Administration; **U.S. DEPARTMENT OF  
HEALTH AND HUMAN SERVICES**; and  
**XAVIER BECERRA**, in his official capacity  
as Secretary, U.S. Department of Health and  
Human Services,  
Defendants.

Case No. \_\_\_\_\_

### DECLARATION OF DR. REGINA FROST-CLARK

I, Regina R. Frost-Clark, a citizen of the United States and a resident of Michigan, declare under penalty of perjury under 28 U.S.C. § 1746 that the following is true and correct to the best of my knowledge.

1. I am over eighteen years old and make this declaration on personal knowledge.
2. I am board-certified in obstetrics and gynecology. I practice with St. John OB/Gyn Associates, part of Ascension Medical Group.
3. I received my M.D. from Wayne State University and did my residency at St. John Hospital and Medical Center in Detroit, Michigan.
4. I am in a hospital owned practice and am often called to the emergency department for consultations.
5. I am familiar with the approval and regulatory changes by the United States Food and Drug Administration (FDA) regarding chemical abortion. Specifically, I am familiar with the relaxing of supervision requirements for administering these very serious drugs, and I am familiar with the relaxed reporting requirements for adverse events related to chemical abortions.
6. I believe these FDA actions will harm women, including my patients, and my practice.
7. As an OB/Gyn, I have treated several women who have suffered complications from chemical abortions.

8. The wider availability of chemical abortion drugs will result in an increase in the frequency of complications related to the drugs' use.
9. In at least a dozen cases, I have treated women who were suffering significant bleeding after taking chemical abortion drugs. Occasionally, women have to be admitted to the hospital for observation due to bleeding complications.
10. In my experience, women who have been given chemical abortion drugs often do not know what they were given or how much of a particular drug they took.
11. In most instances where I treat women who have complications from chemical abortion drugs, they have received it from an abortion facility. Recently a woman told me she obtained these drugs by herself—likely online—and took them without any medical supervision.
12. The FDA's suspension of the in-person dispensing requirement of mifepristone and misoprostol harms women and doctors because it has resulted in an increase in complications.
13. Without an in-person dispensing requirement for chemical abortion drugs, there is a greater chance that women with a molar or ectopic pregnancy will be given drugs that will be ineffectual, leaving them exposed to potentially deadly complications like a rupture or hemorrhage.



14. Similarly, without an in-person dispensing requirement, patients may be given chemical abortion drugs without a confirmed pregnancy or for an inappropriate gestational age.
15. In these instances, patients may avoid seeking appropriate medical care because they are unaware of the risks they potentially face, which puts them in greater danger of complications.
16. Women presenting with complications from chemical abortion pose a challenging situation because I may not have access to their medical history—either because I am unable to access any medical records from prescribers of the chemical abortion drugs or because they obtained the chemical abortion drugs without any medical oversight to begin with. Additionally, the patients themselves usually do not understand what they have been given, how much they have taken, or their follow-up instructions.
17. The lack of patient history and knowledge harms my ability to treat patients. For example, with patients experiencing bleeding, the course of treatment will vary if I believe the bleeding is regular or abnormal cyclical bleeding as opposed to bleeding resulting from attempted abortion.
18. I expect to see more and more women with chemical abortion complications as the use of the drugs increases. Because of the increased complications and the limited information available to me due to the FDA's actions, I fear that I will have greater exposure to liability in my practice.

19. The FDA's actions have led to more confusion for patients and providers. The FDA has forced my colleagues and me to make decisions about patient care based on limited information. It also requires me to spend a lot of time trying to reconstruct patient medical histories to best serve my patients.

20. The FDA's actions make it difficult for patients to have informed consent. Doctors cannot confirm the pregnancy, the location of the pregnancy, or the gestational age without an examination. In abortion clinic settings, it is unclear whether patients are seeing the same physician each time. And often there are no patient follow-up visits with the dispensing facility.

21. Under the current practice by those who prescribe chemical abortion drugs like mifepristone and misoprostol, there is no follow-up or additional care provided to patients and therefore no rapport between patients and their physicians. This makes it difficult to assess who is responsible for these patients when they experience complications.

22. The FDA's removal of the adverse event reporting requirement for all adverse events except death harms my ability to perform evidence-based medicine. I am unable to assess the risks present to women because the FDA's removal of reporting requirements undermines the legitimacy of risk data. For example, Ranitidine, commonly known as Zantac, was pulled from the market due to cancer associations after years of use. Without adverse event reporting, I cannot properly assess the risks that my patients face from abortifacient drugs.

23. I have not reported adverse events that I have witnessed as a result of chemical abortions because the process is so cumbersome. In addition to the burdensome paperwork, it is difficult to file an accurate report given that in many cases I am not certain what the patient was given by the chemical abortion prescriber.

Executed this November 13, 2022.

By:   
Regina Frost-Clark, M.D.

# Exhibit 51

Declaration of Dr. George Delgado

IN THE UNITED STATES DISTRICT COURT  
FOR THE NORTHERN DISTRICT OF TEXAS  
AMARILLO DIVISION

**ALLIANCE FOR HIPPOCRATIC  
MEDICINE**, on behalf of itself, its members,  
and their members, and their members'  
patients; **AMERICAN ASSOCIATION OF  
PRO-LIFE OBSTETRICIANS AND  
GYNECOLOGISTS**, on behalf of itself, its  
members, and their patients; **AMERICAN  
COLLEGE OF PEDIATRICIANS**, on  
behalf of itself, its members, and their  
patients; **CHRISTIAN MEDICAL &  
DENTAL ASSOCIATIONS**, on behalf of  
itself, its members, and their patients;  
**SHAUN JESTER, D.O.**, on behalf of  
himself and his patients; **REGINA FROST-  
CLARK, M.D.**, on behalf of herself and her  
patients; **TYLER JOHNSON, D.O.**, on  
behalf of himself and his patients; and  
**GEORGE DELGADO, M.D.**, on behalf of  
himself and his patients,  
Plaintiffs,

v.

**U.S. FOOD AND DRUG  
ADMINISTRATION; ROBERT M.  
CALIFF, M.D.**, in his official capacity as  
Commissioner of Food and Drugs, U.S. Food  
and Drug Administration; **JANET  
WOODCOCK, M.D.**, in her official capacity  
as Principal Deputy Commissioner, U.S.  
Food and Drug Administration **PATRIZIA  
CAVAZZONI, M.D.**, in her official capacity  
as Director, Center for Drug Evaluation and  
Research, U.S. Food and Drug  
Administration; **U.S. DEPARTMENT OF  
HEALTH AND HUMAN SERVICES**; and  
**XAVIER BECERRA**, in his official capacity  
as Secretary, U.S. Department of Health and  
Human Services,  
Defendants.

Case No. \_\_\_\_\_

## DECLARATION OF DR. GEORGE DELGADO

I, George Delgado, a citizen of the United States and resident of San Marcos, California, declare under penalty of perjury under 28 U.S.C. § 1746 that the following is true and correct true and correct to the best of my knowledge.

1. I am over eighteen years old and make this declaration on personal knowledge.
2. I am board-certified in family medicine and in hospice and palliative medicine.
3. I serve as a medical advisor to the Abortion Pill Rescue Network and as director of medical affairs of Culture of Life Family Services (COLFS) Medical Clinic.
4. I received my medical degree from the University of California, Davis School of Medicine in 1988 and completed my residency at Santa Monica Hospital/ UCLA Medical Center in 1991.
5. I am a Natural Family Planning (NFP) Medical Consultant trained in NaProTechnology. I have also completed a one-year Certification Program in Health Care Ethics with the National Catholic Bioethics Center.
6. I performed the second recorded successful reversal of chemical abortion in the United States.
7. I established Abortion Pill Reversal, a program that connects women who regret taking the abortion-inducing drug, mifepristone (RU-486), and want to reverse the effects of the chemical abortion regimen.



8. I founded the Steno Institute, a non-profit organization, to conduct, promote and publish high-quality, morally sound health science and clinical research in pro-life areas, including chemical abortion reversal.
9. I published the first peer-reviewed article in the medical literature describing the reversal of the abortion-inducing drug, mifepristone (RU-486), using progesterone. The case study, "Progesterone Use To Reverse The Effects Of Mifepristone," presented a series of cases demonstrating successful reversal of mifepristone effects in women who chose to reverse the chemical abortion process. Four of six women who took mifepristone were able to carry their pregnancies to term after receiving intramuscular progesterone 200 mg.
10. I co-authored a peer-reviewed article, "A Case Series Detailing the Successful Reversal of the Effects of Mifepristone Using Progesterone," published in Issues in Law & Medicine, Volume 33, Number 1, 2018. The results of the study concluded that the reversal of the effects of mifepristone using progesterone is safe and effective.
11. Based on my review of peer-reviewed studies, I can attest that there are higher levels of complications from chemical abortion than from surgical abortion. For example, the risk of severe bleeding with chemical abortion is five times higher than from surgical abortion.
12. In my family medicine practice, I continue to see patients one day per week while serving primarily in an administrative role.

13. I treat women with Abortion Pill Reversal in my office in addition to treating women who suffer complications from chemical abortions.
14. I see women who have a great deal of regret from undergoing the chemical abortion drug regimen. They are distressed, sad, and feel terrible about what they have done. While it is rewarding to offer these women a chance at reversing chemical abortion, this is some of the most emotionally taxing work I have done in my career.
15. For example, I spoke with one patient who sought to reverse a chemical abortion after taking mifepristone under duress by the abortion doctor. She recounted that the doctor at the abortion center rushed her to make a decision, placed the pill in her bare hand, and told her to take the pill before it melted in her hand and that it was very expensive. She took the pill because of the duress she was under and immediately regretted the decision. She successfully reversed her chemical abortion. This example illustrates how women and girls are not giving informed consent when undergoing chemical abortion and sometimes coerced into taking these drugs.
16. Given my experience, I expect to see and treat more patients presenting themselves with complications from chemical abortion and seeking reversal of mifepristone.
17. My practice renders early prenatal care to mothers and provides care to babies that are born. In doing so, my practice will bill a patient's insurance company for reimbursement for the costs of care. When my patients have

chemical abortions, there is a tangible financial loss to my practice in losing the opportunity to render professional prenatal care for the mother or to care for babies who are never born.

18. The FDA's elimination of necessary safeguards for pregnant women and girls, such as removing the requirement for an in-person follow-up examination after a chemical abortion, will increase the demands on my time in my family medicine practice and reduce the time I would like to spend with other patients. I will have to treat an increased number of patients due to abortion facilities' failure to provide follow-up care to women and girls.

19. Executed this November 14, 2022.

By: \_\_\_\_\_

George Delgado, M.D.

# Exhibit 52

Declaration of Dr. Shaun Jester

IN THE UNITED STATES DISTRICT COURT  
FOR THE NORTHERN DISTRICT OF TEXAS  
AMARILLO DIVISION

**ALLIANCE FOR HIPPOCRATIC  
MEDICINE**, on behalf of itself, its members,  
and their members, and their members'  
patients; **AMERICAN ASSOCIATION OF  
PRO-LIFE OBSTETRICIANS AND  
GYNECOLOGISTS**, on behalf of itself, its  
members, and their patients; **AMERICAN  
COLLEGE OF PEDIATRICIANS**, on  
behalf of itself, its members, and their  
patients; **CHRISTIAN MEDICAL &  
DENTAL ASSOCIATIONS**, on behalf of  
itself, its members, and their patients;  
**SHAUN JESTER, D.O.**, on behalf of  
himself and his patients; **REGINA FROST-  
CLARK, M.D.**, on behalf of herself and her  
patients; **TYLER JOHNSON, D.O.**, on  
behalf of himself and his patients; and  
**GEORGE DELGADO, M.D.**, on behalf of  
himself and his patients,  
Plaintiffs,

v.

**U.S. FOOD AND DRUG  
ADMINISTRATION; ROBERT M.  
CALIFF, M.D.**, in his official capacity as  
Commissioner of Food and Drugs, U.S. Food  
and Drug Administration; **JANET  
WOODCOCK, M.D.**, in her official capacity  
as Principal Deputy Commissioner, U.S.  
Food and Drug Administration **PATRIZIA  
CAVAZZONI, M.D.**, in her official capacity  
as Director, Center for Drug Evaluation and  
Research, U.S. Food and Drug  
Administration; **U.S. DEPARTMENT OF  
HEALTH AND HUMAN SERVICES**; and  
**XAVIER BECERRA**, in his official capacity  
as Secretary, U.S. Department of Health and  
Human Services,  
Defendants.

Case No. \_\_\_\_\_

### DECLARATION OF DR. SHAUN JESTER

I, Shaun Jester, a citizen of the United States and a resident of Dumas, Texas, declare under penalty of perjury under 28 U.S.C. § 1746 that the following is true and correct to the best of my knowledge.

1. I am over eighteen years old and make this declaration on personal knowledge.
2. I am a board-certified obstetrician and gynecologist and am the Medical Director of Moore County Ob/Gyn in Dumas, Texas. I have been board-certified since 2007.
3. I received my medical degree in 1999 from the Texas College of Osteopathic Medicine at the University of North Texas Health Science Center at Fort Worth.
4. I have a busy medical practice. I am one of three doctors on call. My practice includes cesarean section deliveries, hysterectomies, and other women's health treatments. My practice includes about thirty deliveries each month.
5. A Risk Evaluation and Mitigation Strategy (REMS) is a drug safety program that the U.S. Food and Drug Administration (FDA) can require for certain medications with serious safety concerns to help ensure the benefits of the medication outweigh its risks.
6. I understand that the FDA approved chemical abortion drugs for use in the United States in 2000.



7. I am also familiar with the FDA's regulatory changes regarding chemical abortion drugs, especially the REMS issued in 2016 and associated with the use of mifepristone and misoprostol for chemical abortions.
8. I understand that the FDA approved the use of mifepristone up to 70 days (or 10 weeks) of gestation in 2016, which is longer than the previous standard of 49 days (or 7 weeks).
9. I am familiar with the FDA's suspension and elimination of the in-person dispensing requirements for administering these dangerous drugs in 2021.
10. I am familiar with the removal of the requirement for an in-person, post-abortion office visit, which is when a physician determines whether any fetal parts or other products of conception remain. These visits are essential to ensure that women experience no complications after chemical abortion.
11. I am also familiar with the relaxed reporting requirements for adverse events related to chemical abortions.
12. I believe these FDA actions will harm my patients, women, and women's medicine.
13. I believe that the FDA's approval for using mifepristone at a later gestational age, and the elimination of the in-person dispensing requirement and follow-up visit requirement, are especially dangerous for women.
14. Based on my experience, mothers are often mistaken about how far along they are in pregnancy. According to the Listening to Mothers III survey, 26% of women's due dates are changed.

15. Without an in-person visit to obtain an ultrasound, there is no way to be certain about the gestational age of an unborn child. Women may be further along in pregnancy than is currently acceptable for chemical abortion. Similarly, without an in-person examination, it is impossible to rule out an ectopic pregnancy, which would not be terminated by a chemical abortion and could put women at an increased risk of rupture or even death.
16. Based on my experience treating patients, I believe unsupervised chemical abortions are dangerous and potentially life-threatening especially due to increased risk of hemorrhage and/or infection the further along they are after 6 weeks' gestation.
17. For instance, I treated a woman who traveled from Texas to obtain chemical abortion drugs from Planned Parenthood New Mexico to complete an abortion at 10 weeks' gestation. The woman returned to Texas, suffered from two weeks of moderate to heavy bleeding, and then developed a uterine infection. At the hospital, I provided her with intravenous antibiotics and performed a dilation and curettage procedure. If she had waited a few more days before receiving care, she could have been septic and died. I reported this adverse event to the FDA.
18. The FDA's actions harm my practice by causing unnecessary harm to my patients that could have been avoided by retention and enforcement of the REMS.

19. Doctors like me serve patients as professional health care providers. I provide care to all women and unborn children, and I give them the best professional services possible. Just like other employed obstetrical providers, my hospital will bill for the cost of obstetrical and medical services rendered. When my patients have chemical abortions, I lose the opportunity to provide these obstetrical and medical services to care for the woman and child through pregnancy and bring about a successful delivery of a new life.
20. Additionally, the wider availability of chemical abortion drugs will result in more patients experiencing complications and the number of patients in emergency situations will rise. These situations are naturally higher risk for both the patient and for the physician providing care. In the chemical abortion case that I reported as an adverse event to the FDA, I had no existing patient relationship or prior knowledge of the patient's medical history. Such cases can be a high-pressure, high-risk situation for practitioners like me.
21. The FDA's deregulation of these dangerous drugs increases our exposure to liability.
22. There are many contraindications to prescribing mifepristone, including adrenal failure, steroid use, severe anemia, bleeding disorders, the use of intrauterine devices, undiagnosed ectopic pregnancy, and others. I do not believe telemedicine can rule out all contraindications to prescribing

mifepristone because some of these conditions can only be ascertained with an in-person examination or lab work.

23. Telemedicine does not allow for a critical ultrasound assessment to rule out ectopic pregnancies and verify that the patients are within the 70 days allowed for chemical abortions. In this way, the FDA's loosening of regulations for abortifacient drugs harms women and practitioners by exposing them to increased risk of complications.
24. I believe the relaxed reporting requirements for adverse events related to chemical abortion drugs harm women and physicians because they create an inaccurate and false safety profile for the use of mifepristone and misoprostol. Many women and girls do not fully understand the nature of chemical abortion and the risks that these drugs present to them.
25. The elimination of mandatory follow-up visits after chemical abortion drugs have been administered is also dangerous and harms women and practitioners. Without follow-up visits, physicians cannot identify potential complications like sepsis and hemorrhage, lingering products of conception, and others until the patient is at a critical time or it is too late to help the patient.
26. I care for my patients and give them the best medical care and guidance that I can. I believe that chemical abortions harm women, including my patients, and harm the medical practice. The elimination of REMS critical to ensuring safe use of the chemical abortion drugs prevents doctors from fulfilling their

oath to “do no harm” by permitting the administration of abortifacient drugs to patients without full knowledge or appreciation for the impact those drugs would have on them.

27. As with my patient who suffered an adverse event, it disturbed me that she was not informed that it was not normal to bleed for multiple weeks and that if she had a routine follow-up visit, as required by past REMS, this situation could have been avoided before requiring overnight hospitalization and her being at risk for developing sepsis.

Executed this November 14, 2022.

By:   
Shaun Jester, D.O.